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Autistic Spectrum Disorders as Functional Disconnection Syndrome

Robert Melillo[1] and Gerry Leisman[1,2]

[1]F.R. Carrick Institute for Clinical Ergonomics, Rehabilitation, and Applied Neuroscience of Leeds Metropolitan University, Leeds, UK and [2]University of Haifa, Mt. Carmel, Haifa, Israel

SYNOPSIS

We outline the basis of how functional disconnection with reduced activity and coherence in the right hemisphere would explain all of the symptoms of autistic spectrum disorder as well as the observed increases in sympathetic activation. If the problem of autistic spectrum disorder is primarily one of desynchronization and ineffective interhemispheric communication, then the best way to address the symptoms is to improve coordination between areas of the brain. To do that the best approach would include multimodal therapeusis that would include a combination of somatosensory, cognitive, behavioral, and biochemical interventions all directed at improving overall health, reducing inflammation and increasing right hemisphere activity to the level that it becomes temporally coherent with the left hemisphere. We hypothesize that the unilateral increased hemispheric stimulation has the effect of increasing the temporal oscillations within the thalamocortical pathways bringing it closer to the oscillation rate of the adequately functioning hemisphere. We propose that increasing the baseline oscillation speed of one entire hemisphere will enhance the coordination and coherence between the two hemispheres allowing for enhanced motor and cognitive binding.

KEY WORDS

epigenetic, ADHD, Asperger's, autism, functional disconnection, dopamine systems, gamma oscillations, hemisphericity, dysautonomia

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Reprint address:
Dr. Gerry Leisman
16 Cortelyou Road
Merrick, NY 11566, USA
e-mail: g.leisman@leedsmet.ac.uk

INTRODUCTION

Epigenetic effects on autistic spectrum disorders

Neurobehavioral disorders of childhood that include attention-deficit hyperactivity disorder (ADHD), Asperger's syndrome, and autism have been increasing at epidemic levels over the past two decades. Autism, which ten years ago was still considered a rare disorder that occurred in approximately 1 in 10,000 children in the United States /121/, has recently been estimated to have a prevalence of 1 in 150 in the US /121,123/. Recent estimates have reported a prevalence of autism of 1 in 58 among children born in the UK /157,131/. The increase in autism has gained tremendous attention in the scientific literature and media of late; however, the incidence of other neurobehavioral disorders is also increasing alarmingly. A recent study in Denmark /11/ has shown that ADHD, Tourette's syndrome and obsessive-compulsive disorder (OCD) are rising at approximately the same rate as autism. ADHD is believed to be the leading childhood disorder in the world at this time and the main reason for medicating children. Most disturbingly, experts expect the rise in the use of such medication to increase even more sharply over the next ten years. Many believe that we may be facing the largest childhood epidemic in history, while others believe the increase in the diagnosis of these disorders is due to changing diagnostic criteria and diagnostic substitutions.

Autism reportedly has been considered to have the largest genetic contribution of all the neurobehavioral disorders /145/. However, if this were the case, then autism should actually have a declining or stable prevalence. One of the reasons for this is that most individuals with autism do not

have children. Autism is considered by many leading researchers to have the largest genetic contribution of all multifactor neurodevelopment disorders, with a concordance rate of over 50% between monozygotic (identical) twins compared to less than 5% for dizygotic twins /6,13/.

However, it has been shown that cells can transmit information to daughter cells through non-DNA (epigenetic) inheritance /69/. While behavioral genetics has flourished during the past several decades and the number of genes linked to various normal and abnormal behavioral traits has multiplied, standard theories of genetic transmission have increasingly been challenged. A myriad of non-genetic factors that have been termed 'epigenetic' have been shown to substantially modify or override genetic inheritance /116,63/. The belief that autism is primarily genetic has led to the belief that autism is not correctable /133/. However, recent research has shown that autism is most likely an epigenetic phenomenon rather than genetic, and epigenetic factors can also be passed on to offspring without altering DNA through various mechanisms that affect genetic expression such as DNA methylation /71/. This is an important distinction because epigenetic factors are more amenable to treatment and remediation. As an example of how epigenetics works /69/, "a person's liver cells, skin cells, and kidney cells, look different, behave differently and function differently yet they all contain the same genetic information. With very few exceptions, the differences between specialized cells are epigenetic, not genetic. They are the consequences of events that occurred during the developmental history of each type of cell and determined which genes turned on, and how their products act and interact." The remarkable thing about many specialized cells is that not only can they maintain particular phenotypes for long periods; they can also transmit those phenotypes to their daughter cells. When liver cells divide, their daughters are liver cells. Although their DNA sequences remain unchanged during development, cells nonetheless acquire information that they can pass to their progeny. This information is transmitted through what are known as *epigenetic inheritance systems* (EISs).

Therefore the belief that autism and other neurobehavioral disorders are 'hard-wired' in the brain and exclusive to the brain, that they are strongly genetic, and that they are not correctable with anything short of gene therapy, has been challenged based on recent studies, and the fact that there are reports of autistic children 'recovering'. Herbert /64/ has stated that, "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 /22,33,104-106, 131/. Increases in the rate of autism 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. According to Herbert /64/, she proposes a more conservative description of autism, as a behavioral syndrome with a biological basis and systemic features, influenced by genes and gene-environment interactions. The proposed shift from 'brain based' to 'systemic-genetic' etiology is beginning to allow us to develop a paradigm shift in our thinking about autism. We know that many if not most epigenetic effects occur prenatally and include maternal nutritional status, maternal exposure to drugs, maternal fever, and maternal psychosocial stress. The importance of the prenatal environment to brain development has even challenged the basic assumptions of behavioral genetics /121/.

Neurobehavioral performance issues in autistic spectrum disorders

While there have been significant advances in understanding the many factors that are involved in ADHD, very little has changed regarding its treatment. Stimulant medications, such as methylphenidate (Ritalin, Concerta, Focalin, Metadate, Methylin ER) or dextroamphetamine (Dexedrine, Adderall, Dextrostat, Desoxyn), have been the mainstay of ADHD pharmacology for 50 years. Sadly, these medications are effective for less than 70% of patients. Stimulants can also cause a number of significant side effects; these include decreased appetite, weight loss, decreased growth velocity, as well as dry mouth, constipation,

insomnia, and nervousness. All of this has led to several important questions about autism, ADHD and other neurobehavioral disorders: Whether or not there is an increasing incidence of autism and other neurobehavioral disorders? Whether or not (or to what extent and in what ways) environmental factors contribute to autism, and other neurobehavioral disorders? Whether physical symptoms in autism, ADHD, Asperger's syndrome, etc., are coincidental or a core part of the condition? Whether (and if so in what ways) is it treatable?

One of the most interesting features of children with neurobehavioral disorders is the 'unevenness' of cognitive abilities. For example, it is not unusual to observe high verbal scores combined with low performance scores on intelligence tests. The combined scores may be low to low normal, and many of these children have been considered to be in the mentally retarded range of intellectual ability /77/. One must explain the basis of why unusually high skills are combined with unusually low skills in the same child.

The pattern of strengths and weaknesses in these children appear to present as a fairly reproducible pattern. In addition, the degree of strength of some skills is matched by the degree of weakness of others. This leads us to conjecture a relationship between the strengths and weaknesses. On the other hand, other factors that have been looked at as causative factors, such as inflammation, and white matter growth, do not seem to show this type of relationship. They seem to be non-specific and pervasive, therefore do not seem to be directly related to the unevenness of skills characteristic of these children. This leads us to think that these factors may be a result rather than a cause of the disorders.

We have proposed elsewhere /80,81,83,84/ that the best way to explain the diverse behavioral effects noted in autistic spectrum disorders is by understanding the basis of the condition as a functional disconnection syndrome, not unlike what is seen in sleep, minimally conscious states or as reported in dyslexia /80,81,83-85/. Functional dissymmetry within widespread cortical networks could result in decreased temporal coherence in certain networks while also resulting in enhanced temporal coherence in other functional networks /10/. It would also make sense that enhanced skills are found in the networks with enhanced coherence and reduced skills associated with networks with reduced coherence.

These functional asymmetries or imbalances also seem to be associated with anatomical asymmetries noted only in these children and not others that seem to mirror the functional imbalances /80,81/. Physically smaller areas of activation have been found in various areas of the brain consistently in children with neurobehavioral disorders. These smaller areas seem to represent brain regions that are delayed in development rather than representing any specific form of damage, pathology, and/or atrophy /92/. There has also been noted reduced connectivity between various areas of the brain in children with autism and other neurobehavioral disorders /80,81,83,84/.

The most significant reduction of cortical connectivity appears to be in the corpus callosum /16/. This seems to imply that the most common type of functional disconnection seen in these children is one that involves the two hemispheres. What we also believe is that the hemisphere with reduced coherence is the side responsible for the reduced skill level in various cognitive, motor and sensory abilities which is controlled by that side of the brain, whereas the enhanced capabilities are seen associated with the side of greater coherence /83/. We have also reported reduced connectivity and coherence observed in the longer interhemispheric connections with increased connectivity and coherence with shorter intrahemispheric connections /83,84/ that we theorize leads to the enhanced capabilities such as those seen in savantism.

In autism, ADHD, and Asperger's syndrome it seems that reduced size and coherence as well as connectivity is associated with activation of the right hemisphere. This also seems to be consistent with the reduced cognitive, motor, sensory and autonomic functions that are primarily controlled by the right hemisphere. This is also consistent with research that shows increased neuroendocrine function of the dopamine systems in the brain /3,118/. This hyper-dopamine activity is also associated with an enhanced function of the left hemisphere that has a greater concentration of

dopamine /86/. Dopamine, the most widely studied of all neurotransmitters, is believed to play a crucial role in motivation /35/ and higher-order intelligence /134/ and in most major clinical disorders - including ADHD /46/, autism /118/, bipolar disorder (especially its manic phase) /3/, OCD /1,85/, Parkinson's disease /14/, phenylketonuria /78/, schizophrenia /61/, substance abuse /144/, and Tourette's syndrome /158/. Most of these hyperdopaminergic disorders show a very high comorbidity /54,120/, and many disorders besides autism have shown varying degrees of increased incidence in recent decades /127,128/.

Neuroimaging /64,65/ and genetic studies /20,74/ 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 /21,56,73/. Genetic studies suggest intriguing overlaps /70/ such as between autism, Tourette's syndrome and various autoimmune diseases /18/. Similar *in utero* infection and maternal antibody factors may be involved in the patho-etiology of a variety of neurodevelopmental and neuropsychiatric disorders /37/. 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 the definition of autism.

MOTOR AND SENSORY FUNCTION IN AUTISTIC SPECTRUM DISORDERS

Problems of interhemispheric interaction

In general, dopaminergic (DA) systems tend to be more involved in motor than in sensory behavior, in voluntary motor behaviors more than in automated ones, in actions directed at distal rather than proximal space, and in motivationally oriented ('wanting') rather than consummatory ('liking') behavior. As a corollary to its role in distally oriented, sequential voluntary motivational behaviors, DA systems also appear to be critically involved in what is referred to as 'executive' intelligence /43,107,118/ which includes such components as working memory and cognitive shifting and is highly related to fluid/general intelligence /118/. Dopamine agonists in rats and monkeys reduce social behaviors such as grooming and play /112,113,135/ and the dopaminergic personality can be best described as combining social detachment with high motivation and achievement and a high internal locus-of-control, i.e., the belief in one's ability to control one's destiny /39,42,119/.

Although DA may be important in 'agentic extraversion' or social interactions that help achieve one's own personal goals /42/, genuine social/emotional skills appear to rely more on noradrenergic and serotonergic circuits that predominate in the right hemisphere /119,115,148, 155/. The primary symptoms in autism, ADHD, and Asperger's syndrome of reduced social ability, nonverbal communication, hyperactivity, perseverative behavior as well as reduced gross motor, enhanced fine motor skills, and enhanced local and reduced global visual and auditory processing all seem to be consistent with right hemisphere function combined with enhanced left hemisphere function. In fact all of the enhanced capabilities that have been associated with savant syndrome are left hemisphere skills and all deficiencies of the same syndrome appear to be right hemisphere skills. Somatosensory processing for action guidance can be dissociated from perception and memory processing. The dorsal system has a global bias and the ventral system has a local processing bias. Individuals with autism illustrate the point showing a bias for part over wholes. Lateralized differences have also been noted in these modalities. The multi-modal dysfunction observed may suggest more disordered interhemispheric communication /80,81,83,92/.

Sensory motor interaction: Global vs detail processing and its lateralization in autistic spectrum disorders

Dijkerman and de Haan /44/ propose that somatosensory processing for the guidance of action can be dissociated from the processing leading to perception and memory. Leisman /79/ showed that voluntary movement, like all other movements, consists of operations in time and space specified by physical parameters. When, for

example, a person lifts a cup to his lips, the trajectory of the teacup, force vectors, acceleration, and velocity at every point, total length of the path, locus of origin, and the time of onset specify his voluntary movement. Neurologically normal adults usually carry out voluntary movements of this kind quickly and precisely and without information concerning the total mass or its contents.

There are two types of explanations for the surprising precision with which we move our limbs. One is that the motor system calculates in advance the values of movement parameters sufficiently accurately to assure successful performance. The other explanation is based on the fact that every muscular contraction changes the state of receptors in muscles and tendons. These receptors measure parameters of voluntary contraction and transmit this information to the motor system. The motor system is then thought to control voluntary contraction under the guidance of sensory feedback from these receptors. Although there is no contradiction between these two explanations there is disagreement as to the relative importance of specific motor commands versus sensory feedback. Another equally important dimension in the understanding of the organization of voluntary motor control is the question of the levels of the central nervous system at which the desired values of voluntary contraction parameters are calculated or the extent to which voluntary contractions are automatic because man is able to consciously vary the parameters of voluntary contractions in an infinite number of ways.

Dijkerman and de Haan /44/ suggest that the posterior parietal cortex subserves both perception and action, whereas the insula subserves perceptual recognition and learning. The authors infer a close relationship to the dorsal and ventral visual systems and possibly the auditory system. The authors have provided an intellectual genealogical extension of Milner and Goodale /57,94/ who reinterpreted Ungerleider's and Mishkin's /149/ distinction between the 'what' and 'where' visual systems. Ungerleider and Mishkin /96,149/ suggested that the 'ventral' visual stream (geniculostriate pathway projecting to the inferotemporal cortex) subserves object identification, while the 'dorsal' stream (projections from the striate cortex and colliculi to the posterior parietal cortex) subserves object localization. This suggests that the function of the dorsal stream is better described as mediating visually guided actions. Thus, they replace Ungerleider's and Mishkin's 'what' versus 'where' distinction with a distinction between 'what' versus 'how'.

In the visual system we see the dorsal and ventral stream process different types of visual information. Specifically, the dorsal system has a global bias focusing on lower spatial frequency information, whereas the ventral system focus has a local processing bias utilizing higher spatial frequency information. The dorsal system tends to focus on global form whereas the ventral system focuses on details or parts of wholes. Autism is an excellent example of increased weighting of one system and diminished processing of the other. Frith /51/ proposed a theory of weak central coherence in autism (ASD). Additionally, her theory of *enhanced perceptual discrimination* /136/ attempted to explain the uneven profile of abilities and difficulties in ASD. Central coherence refers to the ability to put information together to extract meaning, to remember the gist of a story rather than its details. Individuals with ASD show a bias for part over whole - often excelling at noticing and recalling detailed information. Perception and processing features are believed to be superior, possibly at the expense of processing global information.

Mottron and colleagues /99/ showed this same type of bias in the auditory systems of individuals with autism along with sensory motor deficits explained partly by a more ventrally based sensory motor system focusing more on action and less on perception. Individuals with autism are believed to have poor body schema and spatial localization of body parts. Many individuals with autism cannot identify their body parts in a mirror /97/. Even if they know the word 'nose' they may still identify the wrong body part. They have poor proprioception and are generally clumsy /95/. These examples emphasize increased action and decreased perception. This parallels what we see in vision and audition with the emphasis on the ventral system and decrease in the dorsal system.

The mirror neuron system is dysfunctional in

individuals with autism /60/. This system also seems to utilize similar processes to recognize movements in an implicit manner for the extraction of meaning of intent and emotion. In normal individuals, motor activity suppresses *mu* activity in the sensory motor cortex, but it is also suppressed in normal individuals when they observe someone else performing a motor act /109/. In individuals with autism we see that the *mu* wave is suppressed only with their own actions but not when they observe others. This again would seem to show unevenness in sensory/motor modalities with an emphasis on action and diminished perception.

Lateralized differences have also been noted in these modalities. It has been well established that in vision, the right hemisphere processes information primarily with the more globally focused dorsal system /84,92/. The left hemisphere tends to focus on detail similarly to the ventral visual system. The same right/left hemisphere differences exist in the auditory system. The right hemisphere is more spatially oriented toward the dorsal 'where' and the left hemisphere is focused on the ventral 'what'. This is also believed to exist within the somatosensory system where the right hemisphere is more focused on dorsal perceptual/sensory systems and proprioception as well as implicit knowledge of egocentric relationships, and the left hemisphere is more focused on action or motor activity and conscious awareness of body parts. The multimodal dysfunction observed in ASD may suggest more an issue of hemispheric function.

ADHD, substance abuse, schizophrenia, and OCD may all involve excessive activity in the medial (mesolimbic and cortical) DA systems /103, 138,150/. Mania may involve activation of both the medial and lateral cortical DA systems /18,23/ and Tourette's syndrome may involve overactive DA systems in the basal ganglia /23/.

By contrast, autism may be associated with brainstem abnormalities to a greater extent than these other disorders /53,110,125/. All 'hyperdopaminergic' disorders are characterized by heightened motor or cognitive activity that entails some basic or higher-order stereotypy /124/. It may involve the rocking and whirling of an autistic child, the uncontrolled outbursts in Tourette's syndrome, the bizarre rituals in OCD, the racing thoughts in schizophrenia, or the addictive behavior in substance abuse. All of these disorders are accompanied by at least moderate deficits in social competence, and all are correlated with each other well in excess of their predicted values. In addition, these disorders all reflect a relative overactivation of the left hemisphere, which is relatively deficient in social and pragmatic communicative skills /115/, and has a greater DA concentration to begin with /50,148/. This left hemispheric activation is particularly true for mania /28,50,124/, schizophrenia /36,50/, Tourette's syndrome /27,59,117,129/ and probably autism as well.

Three sets of findings comprise the main evidence that overactivation of DA systems represents the most characteristic brain dysfunction in autism. They are: (1) the link between hyperdopaminergic activity and the various behaviors characteristic of at least high-functioning autism; (2) the relation between autistic deficits and right-hemispheric dysfunction; and (3) pharmacological evidence, including assays of DA activity and efficacy of anti-DA treatments. In regard to autism, temporal, parietal and frontal, anterior cingulate and right hemisphere hypoperfusion has been noted /24,29,64,100,160/. According to Herbert /119/:

> "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. In fact, researchers now think that the ultimate defect in autism may be related to the connections (or "circuits") made within the brain rather than to a single, impaired brain structure. Recent physiological, anatomical, and genetic experiments have characterized autism as a disorder of *functional connectivity*, such that individual brain regions may not be working together in a coordinated fashion."

There exists a high co-morbidity of many neurobehavioral disorders /159/, such as the case with disorders like ADHD and schizophrenia, OCD, and Tourette's syndrome. The most likely cause of this disruptive coordination is a dys-

function and/or imbalance in the thalamocortical system. The thalamocortical system has evolved as the most efficient solution for implementation of temporal coherence across areas of the brain that not only serve different roles of reality emulation, but which are also physically very distant from each other. These cortical regions include sensory, motor and association areas; the latter is the largest part of the cerebral cortex in *Homo sapiens*. These areas provide a feedforward, feedback reverberating flow of information. Studies indicate that 40 Hz is the coherent neuronal activity large enough to be detected from the scalp, and is generated during cognitive tasks /76,142/. This 40 Hz activity reflects the resonant properties of the thalamocortical system, which in itself is endowed with intrinsic 40 Hz oscillatory activity.

40 Hz coherence waves are related to consciousness. Electroencephalography has demonstrated a role of these signals for cognitive functions including visual perception, attention, learning and memory /87,114/. During auditory processing, the magnetoencephalogram has identified oscillatory activity in higher frequency ranges and with a more discrete localization than the electroencephalogram /66/. Gamma-band activity increases have been observed in the putative auditory dorsal and ventral processing streams during the processing of auditory spatial and pattern information, respectively /87/. Additional gamma-band activity has been found over the frontal cortex during top-down tasks /87,101/.

TOWARDS A UNIVERSAL THEORY OF AUTISTIC SPECTRUM DISORDERS

Oscillatory activity in the gamma range may serve to assess the temporal dynamics of cortical networks and their interactions. We believe that all of these theories are essentially interrelated and can be explained by one universal theory. This theory is that lack of synchronization or temporal coherence between the two hemispheres and/or various large areas of the central nervous system leads to a lack of optimized communication between these areas. This lack of optimized activity leads to underconnectivity between brain regions and these two factors result in a functional disconnection syndrome. This disconnection is due to one hemisphere being more active and functioning at a higher oscillation rate. This prevents the ability of the two hemispheres to synchronize, bind and share information /80,83,84,146/ thereby theoretically impeding temporal binding of distant neurons. This forces the individual to choose between different virtual sensory images of the world, and due to cortical-cortical inhibition the underactive areas are suppressed or impaired, leading to reliance on information primarily from one hemisphere.

CLINICAL ASPECTS OF SYNCHRONOUS GAMMA-BAND ACTIVITY

Synchronous gamma-band activity in schizophrenia

Various studies have begun to look at the concept of functional disconnection in a range of different conditions, such as sleep /38/ and dyslexia /80,83,84,106/.

There has been a convergence of models describing schizophrenia as a disconnection syndrome, with a focus on the temporal connectivity of neural activity. Synchronous gamma-band (40 Hz) activity has been implicated as a candidate mechanism for the binding of distributed neural activity /4,5/. To the authors' knowledge, this is the first study to investigate 'gamma synchrony' in first-episode schizophrenia. Andreasen and colleagues coined the term 'cognitive dysmetria' to emphasize the temporal dimension of neural disconnection in schizophrenia. They proposed that a "disruption to fluid coordination of mental activity" at the 'nanosecond' time scale impairs the ability to integrate and contextualize incoming sensory input in order to form an appropriate and adaptive response. Andreasen and colleagues hypothesized that a lack of connectivity in cortical-cerebellar-thalamo-cortical circuitry underlies cognitive dysmetria. An example of this activity is to be found graphically described in Figure 1 and serves as a comparison point for a discussion of functional disconnectivities and synchronous gamma-band activity in autistic spectrum disorders.

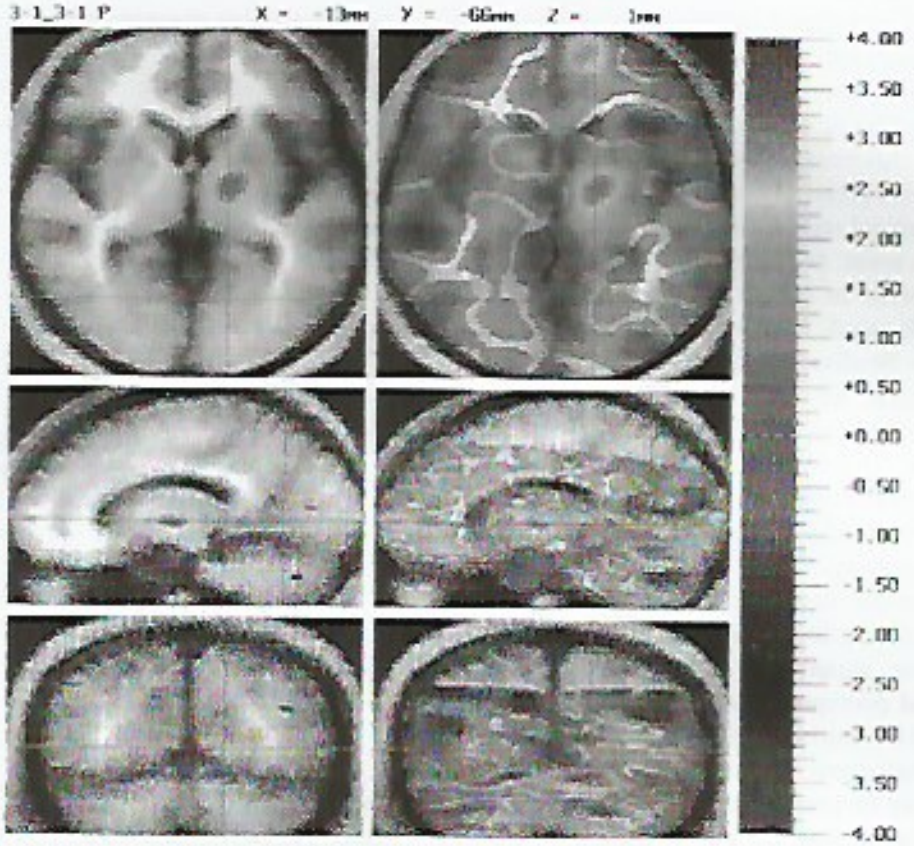


Fig. 1: The results of the randomization analysis /4/ used to identify the specific regions where the schizophrenic patients differed from the normal volunteers. Regions in upper wavelengths indicate lower flow in patients during the practiced recall task, while regions in lower wavelengths indicate higher flow in patients. Results are portrayed using the value of the associated t statistic, shown on the bar on the right. Statistically significant areas where the patients have decreases in flow include left frontal (transaxial view), left thalamus (transaxial and sagittal views), and bilateral cerebellum (sagittal and coronal views). Patients with schizophrenia have reduced flow in cerebellar and prefrontal regions during both a practiced and a novel recall task. Significant thalamic abnormalities were noted on the right for the novel task and on the left for the practiced task. Schizophrenia then is probably not best conceptualized as a disease of a single brain region, but rather a disease involving complex circuits displaying different patterns of disruption depending on the task. Multiple nodes in the network were found to have decreased flow, reflecting decreased optimization in the interconnections between nodes. Andreasen and colleagues indicated that the brains of schizophrenics do not form homogeneous connections and networks efficiently resulting in functional disconnectivities. © 1999 Elsevier; reprinted with permission from /4/.

Synchronous gamma-band activity in autistic spectrum disorders in relation to hemisphericity

In the case of autistic spectrum disorders we assume that the underactive and suppressed hemisphere is, primarily the right. This fact can be used to assist in explaining the other two primary theories of the cause of autistic spectrum disorder, lack of central coherence /89,102/ and theory of mind /48,72,143/. In the theory that involves the lack of central coherence, individuals with autistic spectrum disorders seem to preferentially engage in a local processing mode that focuses them on detail with difficultly in being able to place themselves in the context of the 'bigger picture'. It is well established that the left hemisphere is primarily responsible for local processing and the right hemisphere is involved in global processing. Social

comprehension involves empathy for others' experiences and appropriate responses to non-verbal cues. Previous research using magnetic resonance imaging (MRI) has suggested a relationship between brain morphology and psychiatric syndromes, such as ADHD, that typically entail social difficulties. The right hemisphere has been specifically associated with social skill deficits, and numerous studies have also associated ADHD with social skill deficits. No studies, however, have examined the association of ADHD subtype with both social comprehension and right-hemisphere morphology.

In one study /93/, 59 children (6-12 years old) underwent MRI examination, from which the right hemisphere was classified into four morphologic subtypes. Children were also grouped by ADHD subtype or clinical control status. From the Behaviour Assessment System for Children (BASC) items, a social comprehension subscale was constructed. Analyses revealed significant differences in social comprehension based on ADHD subtype. Differences in social comprehension based on ADHD status were especially pronounced in children with atypical right-hemisphere morphology. Thus, the diagnosis of ADHD might be associated with deficits in social comprehension, especially for those children with atypical right-hemisphere morphology. In children manifesting right hemisphere dysfunction with attention-deficit disorder but without hyperactivity, most evidence supports the view that right-hemisphere-type activity, relying more on serotonin (5-HT) and norepinephrine (NE) transmission, is relatively deficient in autism, thereby shifting the neurochemical balance even more toward the DA-rich left hemisphere /34,117/. For example, deficiencies in social and emotional behavior that follow damage to the right hemisphere are very similar to those in autism /40,115,155/. Several abnormalities found in autism - deficient *theory of mind*, impaired processing of facial expression, deficient prosody, impaired judgment of speaker intent (e.g., humor and inferencing), and superior performance on the Embedded Figures Test, which measures the ability to focus on local details to perceive forms embedded in noise - are particularly indicative of deficient right-hemispheric and/or enhanced left-hemispheric capabilities /62,90,91,111,118,132/.

Studies /62,111,156/ have also shown that individuals with ADHD and autism often show deficient right hemisphere abilities that seem to resemble those in patients with right hemisphere damage and stroke. Ozonoff and Miller /111/ examined the contribution of the right hemisphere to the communicative impairments of autism. They administered pragmatic language tests, sensitive to right-hemisphere damage, to non-retarded autistic adults, and to age- and intelligence-matched controls. Autistic subjects performed significantly less well than controls on all measures, replicating the results of Rumsey and Hanahan /130/. The performance of the autistic group on the three tasks was also similar to that of right-hemisphere stroke patients reported previously by Molley and colleagues /98/.

Additionally, children with ADHD show various types of hemi-neglect, visual, motor and tactile symptoms. This type of neglect is seen consistently in individuals with right hemisphere dysfunction and damage, further leading to the conclusion that the symptoms associated with ADHD and autism may reflect a right hemisphere deficit. Despite the similarities between autistic symptoms and those following right-hemispheric damage, there is no evidence for actual damage to the right hemisphere in most persons with autism. Rather, it is more likely that the behaviors typical of the DA-rich left hemisphere are simply magnified when the DA content of the entire brain is increased. Also, in theory of mind, it is thought that individuals with autism primarily lack mind reading capacities or the ability to communicate non-verbally with other individuals. They cannot read body posture or facial expressions that non-verbally and subconsciously relay information especially about emotional states to other individuals. They seem to be literal in their receptive and expressive communication abilities and they lack prosody in speech. They also seem to be unable to hear changes in tone and prosody especially related to emotion. All of these abilities are well recognized to be right hemisphere based.

However, we will also see that when one hemisphere is suppressed or inhibited the other hemisphere's abilities may become enhanced. This

may be an explanation for savant syndrome in which most of the exceptional abilities - math calculation, fine motor skills, imitation, music playing and memorization abilities, hyperlexia, visual imagery, and puzzle ability, etc. - seem to be left hemispheric in nature. The level of increase in left hemisphere skills seems to be negatively correlated with decreases in right hemisphere skills. Research employing transcranial magnetic electrical stimulation has demonstrated that inhibition of one hemisphere in some individuals seems to increase abilities in the opposite hemisphere /49, 137/.

THE ROLE OF DYSAUTONOMIA AND FUNCTIONAL DISCONNECTIVITY IN AUTISTIC SPECTRUM DISORDER

Children with neurobehavioral disorders exhibit a wide range of symptoms that are not limited to cognitive, motor or sensory function; they also present with significant autonomic and immune regulatory issues. The severity of immune dysregulation seems to parallel the severity of the other functional deficits. Until recently it was thought that the digestive and immune dysfunctions associated with autistic spectrum disorders were purely coincidental and therefore not intrinsically related to the neurobehavioral disorder. However, it is now more widely recognized that dysautonomia and immune dysfunction are in fact directly related to autistic spectrum disorder. The relationship between the immune and nervous systems is poorly understood. Many of the reported gastrointestinal abnormalities are of an immune character, such as altered mucosal immunity /7,8,52,147/, and atypical immune responses to certain dietary components have also been reported (see Melillo and Leisman /22/ for a full review).

Central nervous, gastrointestinal and immune systems all interrelate. 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 /8,9,15/. It is well recognized that children with autism and other neurobehavioral disorders seem to have an immune profile that has shifted toward autoimmunity. Why this is the case is a mystery to many. However, we believe that it is also a product of the same functional disconnectivities described earlier, with right hemisphere dysfunction being most evident. The unique profile that is most commonly seen in these children in dietary, digestive, and immune function is manifest typically in children who are 'picky eaters' often restricting their diet to specific foods. They often have poor sense of taste and smell and choose foods primarily by the way they feel and look rather than the way they taste and smell. They have many food aversions. In one study /17/, for example, 21 participants (10-18 years) with autism were compared with 27 matched control participants with typical development. Taste identification was tested with sucrose, NaCl, citric acid, and quinine solutions. Electrogustometry detected thresholds and olfactory identification was evaluated with 'Sniffin' Sticks'. The investigators found that participants with autism were significantly less accurate than control participants in identifying sour tastes and marginally less accurate for bitter tastes, but they were not significantly different in identifying sweet and salty stimuli. Taste detection thresholds by electrogustometry were equivalent. Olfactory identification, however, was significantly worse among participants with autism. Bennetto and colleagues /17/ concluded that true differences exist in taste and olfactory identification in autism. There exists impairment in taste identification with normal detection thresholds suggesting cortical rather than brainstem dysfunction.

Digestive symptoms have also been reported in autistic spectrum disorders that have included intestinal hyperpermeability, reduced motility, and decreased secretion of digestive acids and enzymes; these individuals are often constipated and appear to demonstrate digestive malabsorption /88,126, 134,140/. In the immune system individuals with autistic spectrum disorders appear to be overly sensitive and prone to autoimmune regulated disorders. They seem to have poor detoxification profiles that seem to be related to poor digestion and autoimmunity /47/. Additional symptoms as indicated earlier in this paper include poor socialization, non-verbal communication, empathy, and gross motor development, and low muscle tone, poor gross spatial awareness, uncoordination,

abnormal gait and posture, poor attention and impulse control, and enhanced local processing and reduced global processing of visual and auditory input.

Autonomic functional disconnectivities

The role of the insula

The varied symptoms reported above can be ascribed to a single primary deficit and source based on the notion of functional disconnection, the result of an especially underactive right hemisphere in autistic spectrum disorders. An area implicated as a dysfunctioning link between the motor, sensory, immune, and digestive symptoms is the right insula cortex and its relationship with the anterior cingulate region. Individuals who have grown up with autism who have written of their experiences often describe feeling disconnected from their physical bodies. They report not feeling their bodies well. In fact some have said that they did not even realize they had a body at all /58,139/. This would also explain why many of these children do not seem to react to pain when they injure themselves.

Beside the right hemisphere reportedly being responsible for spatial awareness and gross motor control, it also possesses the sensory map for the whole body /96/. In fact, the right hemisphere is more sensory by nature and has therefore greater influence on attention mechanisms that utilize sensory input /92,79/. This is related to the neglect syndromes frequently observed with right hemisphere damage. Additionally, the right frontal insula appears singularly associated with the awareness of the individual of his body and its regulation. Damasio /38/ has referred to this notion of body awareness as 'somatic markers' that may be at the foundation of recognizing one's own emotional state, in turn serving as a foundation for reading emotions in others. Examining this notion further, studies /30,31/ have shown that individuals who are better at perceiving their own heart beat are those who have the most active and larger, right frontal insula cortex. The insula cortex on the right side is also believed, with the anterior cingulate, to regulate the ability to empathize with others, and it is also part of the mirror neuron network that allows us to understand the feelings and intentions of others. In a follow-up study Critchley *et al.* /32/ found that people with greater empathy have more gray matter in their right frontal insula.

Interoceptive mechanisms

Interoception is a separate realm of somatic sensations that is oriented inward and has two sources of input. The first is the internally mapped state of one's body. These are conscious sensations of hunger, thirst, heart rate, stomach contractility, etc. The information arises from receptors that map 'gut feelings'. In other words, just as the parietal and frontal lobes have sensory and motor homunculi, the insula contains visceral homunculi. The second source of interoceptive maps consists of different classes of receptors found on the body's surface, and includes the teeth, gums, and tongue. These receptors carry information about the 'homeostatic' condition of the body, including temperature, pain, itching, muscle ache, sexual arousal, crude touch, and sensual touch, mainly mediated through the small unmyelinated C fibers.

In primates, interoceptive information is elaborated through a rich set of mappings in the insula cortex. In humans it is the richest by far. After 'reading' the state of one's body from both the left and right insulae, only the human brain performs an additional level of integration. The information from both insulae is routed to the right frontal insula /103/. The insula cortex also serves as the primary cortical sensory area for the vestibular system and the afferent input from the gut and autonomic nervous system /26/. It is also involved with the interpretation of taste /122/ and smell /45/, as well of control of digestive function /41/ through its interaction with the orbital frontal cortex and the solitary nucleus. It helps regulate hedonic experience and helps to reinforce goal-directed reward behavior.

A unifying view of the role of von Economo neurons in autistic spectrum dysautonomia, asocial behavior, and cognitive function

The cells that are found prominently in this area of the brain are the Von Economo cells /154/ that appear to be some of the most phylogenetically

sophisticated cells in the brain. Von Economo neurons (VENs) are large, bipolar neurons located in layer 5 of the anterior cingulate cortex (ACC) and fronto-insula (FI) cortex. Unlike most neuron types, VENs are present in the great apes but are absent in lesser apes, Old and New World monkeys, and prosimians /108/. This suggests that they arose in the hominoid clade within the last 15 million years. The volume of the soma is much larger in humans than in apes, and stereological counts indicate that these cells have proliferated in the human line of descent /108,154/. The recent emergence of this cell type, as well as its localization to subregions of the prefrontal cortex, suggests its involvement in sophisticated cognitive behaviors. This suggests that studies of these cells may provide insights into human uniqueness and origin. Furthermore, because the force of natural selection has had only a relatively short time to shape their functioning and integration with other cell populations, the VENs may be particularly vulnerable to dysfunction. Thus, knowledge of the morphology of the VENs may be useful in evaluating possible pathological variants in neurogenetic and neuropsychiatric disorders. They are found only in humans, some non-human primates such as bonobos, in dolphins, and possibly in elephants. These cells seem to regulate some higher-level cognitive functions especially those associated with socialization and non-verbal communication. Evidence suggests that the function of the VENs may be to provide a rapid relay to other parts of the brain of a simple signal derived from information processed within the FI and ACC.

Functional magnetic resonance imaging studies indicate that the FI and ACC are co-activated when subjects experience social emotions, such as empathy /140/, guilt /138/, violation of social norms /19/, deception /141/, and humor /154/. As yet, we do not know the mechanisms responsible for the differentiation of the complex social emotions that activate the FI and ACC, but we do know that the VENs are a recently evolved population that probably serves to relay output of the processing within the FI and ACC to other brain structures. Their large size suggests that the VENs may relay a fast intuitive assessment of complex social situations to allow the rapid adjustment of behavior in quickly changing social situations /2/. They can thus be seen as an adaptation supporting the increased complexity of hominoid and especially human social networks. The receptors that are found in these cells are the type 2b serotonergic cells and these are only found in one other place in the human body, the gut musculature that regulates peristalsis and gut motility. It is thought /154/ that contractions of these muscles also give powerful feedback to the insula cortex, especially the right, which uses this information to provide 'gut reactions' and feelings that form the foundation of intuition.

Right hemisphere dysfunction and immunity

The connection between the right hemisphere and the immune system has also been well documented in the literature. The right hemisphere's role in regard to the immune system is immunosuppressive (cf. /22/). It has been shown that with lesions to right frontal areas, there is a significant increase in the production of lymphoid tissue as well as increased production and reaction of IgE and IgG cells, T-cells, and of inflammatory chemicals such as cytokines /151/. Therefore, with a dysfunction of the right hemisphere, we would expect that the child's immune system would be shifted toward autoimmunity with increased function of the left hemisphere's control of the immune system. Lastly, regarding inflammatory bowel changes and intestinal hyperpermeability of the bowel that has been noted /52/, regulation of the sympathetic nervous system and its interaction with the parasympathetic nervous system will affect bowel function. For normal digestion to take place there needs to be a balance of activation favoring the parasympathetic system. If the sympathetic nervous system is uninhibited then it will have a significant effect on bowel function. With increased sympathetic activity gut functioning is affected in four primary ways: 1. reduced secretions of acid and digestive enzymes which would reduce the chemical breakdown of food, especially proteins; 2. reduced peristaltic contractions that would slow motility also affecting the mechanical breakdown of food; 3. reduced blood flow to the stomach and intestinal lining reducing absorption of nutrients,

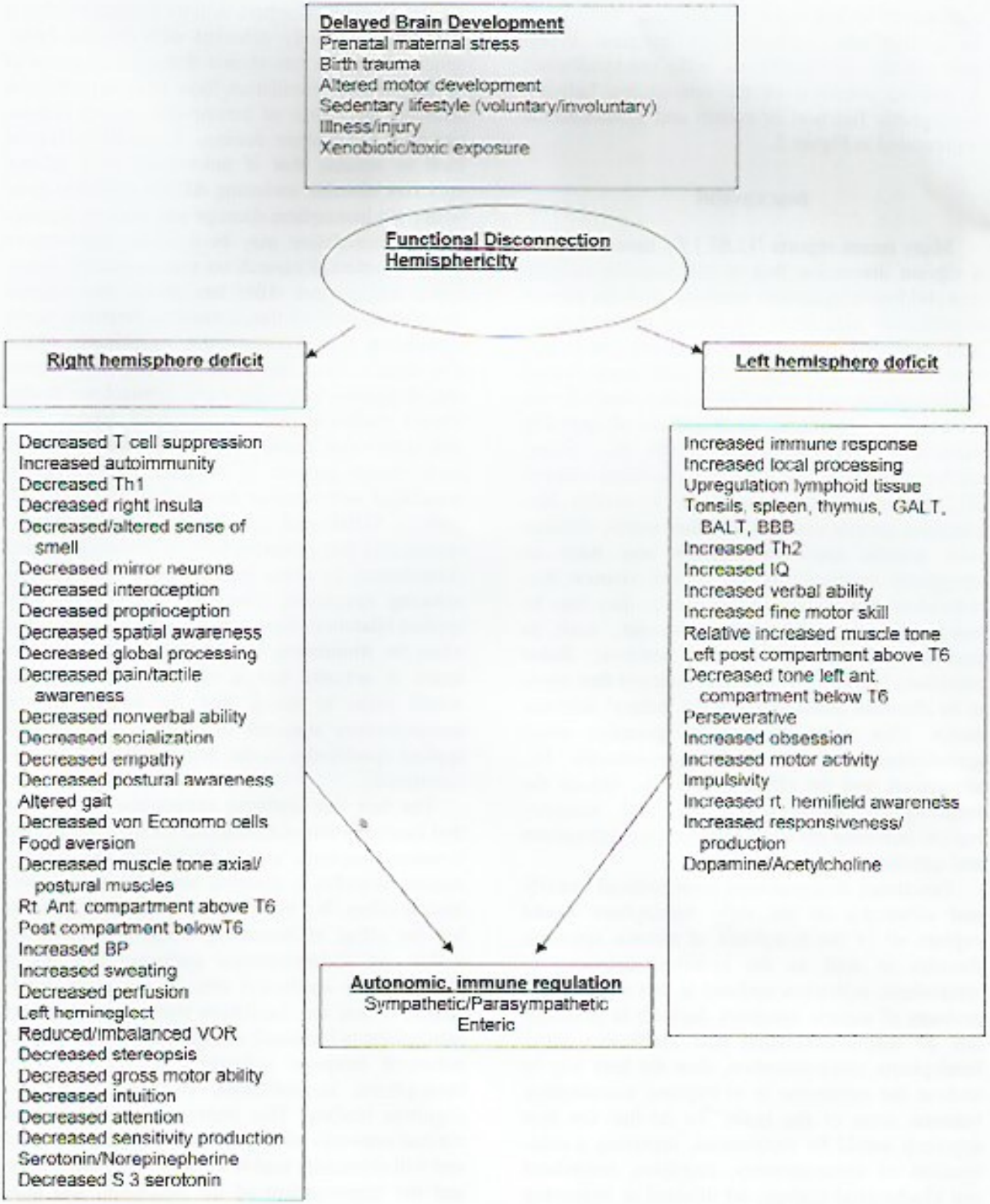
and increasing fragility of the intestine and stomach lining that may contribute to intestinal hyperpermeability, also known as 'leaky gut syndrome'. A graphic overview of the relationship between hemispheric function in autism and dysautonomia is presented in Figure 2.

DISCUSSION

Many recent reports /12,67,153/ have generated a vibrant discussion that is still ongoing in print that children with autistic spectrum disorder excrete significantly high levels of urinary methylmalonic acid compared to age-matched controls, an indication of a functional vitamin B_{12} deficiency. Raised methylmalonic acid secretion is often coupled with elevated homocysteine, the metabolic abnormality associated with functional vitamin B_{12}, folate, and/or vitamin B_6 deficiency. Functional vitamin B12 deficiency may track back to certain biochemical genetic markers. In other words, children with autistic spectrum disorder may have an epigenetic susceptibility for altered vitamin B_{12}-dependent metabolism. Alternatively, they may be manifesting a malabsorption disorder, such as parietal cell insufficiency of intrinsic factor secretion. Vitamin B_{12} is a large nutrient that needs to be absorbed in the absence of a 'helper', intrinsic factor. This raises all sorts of questions about gastrointestinal (GI) physiology, vitamin B_{12} absorption, and the effect vitamin B_{12} has on the neurological system beyond the frank immunological influence between ileal nodular hyperplasia and autistic spectrum disorder.

Functional disconnection with reduced activity and coherence in the right hemisphere would explain all of the symptoms of autistic spectrum disorder as well as the observed increases in sympathetic activation outlined in this paper. If the problem of autistic spectrum disorder is primarily one of desynchronization and ineffective interhemispheric communication, then the best way to address the symptoms is to improve coordination between areas of the brain. To do that the best approach would be multimodal, including a combination of somatosensory, cognitive, behavioral and biochemical therapy, all directed at improving overall health, reducing inflammation and increasing right hemisphere activity to the level that it becomes temporally coherent with the left hemisphere. Research has shown that various forms of somatosensory stimulation have been successful at reducing symptoms of hemispatial neglect following right hemisphere damage. It would be logical then to assume that if individuals with autistic spectrum disorder including ADHD resemble those with right hemisphere damage and neglect, somatosensory stimulation may be a useful treatment in these disorders. Research on somatosensory stimulation and neglect /106/ has shown that various modalities, such as transcutaneous electrical nerve stimulation (TENS), vestibular, optokinetic, vibration, and tactile stimulation can all reduce hemispatial neglect following right hemisphere stroke. Recent studies as well as anecdotal reports have also shown that sensory and motor-based therapies have shown success in reducing the symptoms associated with various neurobehavioral disorders such as ADHD and autism. Studies have demonstrated /91/ that somatosensory stimulation applied contralateral to brain lesions were successful in reducing symptoms; when the stimulations were applied bilaterally there was a negligible effect, and when the stimulation was applied ipsilateral to the lesion it actually had a worsening effect. This would seem to imply that the benefit of the somatosensory stimulus is only seen when it is applied specifically to the hemisphere that is dysfunctional.

The fact that applying stimulation to the side that increases stimulation of the normal hemisphere worsens symptoms would imply that the somatosensory stimulus is creating some form of equilibrating effect. We think that the increased stimulus has the effect of increasing temporal oscillations within the thalamocortical pathways bringing it closer to the oscillation rate of the good hemisphere. When the oscillation rate of the deficient hemisphere is increased enough by the stimulus the enhanced temporal coherence between the two hemispheres re-establishes communication and cognitive binding. This improved coordination of cortical networks addresses the underlying problem and will eventually lead to enhanced neuroplasticity and the improvement of the functional and anatomical connectivity of the two hemispheres.


Delayed Brain Development
Prenatal maternal stress
Birth trauma
Altered motor development
Sedentary lifestyle (voluntary/involuntary)
Illness/injury
Xenobiotic/toxic exposure
Functional Disconnection Hemisphericity
Right hemisphere deficit
Left hemisphere deficit
Decreased T cell suppression
Increased autoimmunity
Decreased Th1
Decreased right insula
Decreased/altered sense of smell
Decreased mirror neurons
Decreased interoception
Decreased proprioception
Decreased spatial awareness
Decreased global processing
Decreased pain/tactile awareness
Decreased nonverbal ability
Decreased socialization
Decreased empathy
Decreased postural awareness
Altered gait
Decreased von Economo cells
Food aversion
Decreased muscle tone axial/ postural muscles
Rt. Ant. compartment above T6
Post compartment belowT6
Increased BP
Increased sweating
Decreased perfusion
Left hemineglect
Reduced/imbalanced VOR
Decreased stereopsis
Decreased gross motor ability
Decreased intuition
Decreased attention
Decreased sensitivity production
Serotonin/Norepinepherine
Decreased S 3 serotonin
Increased immune response
Increased local processing
Upregulation lymphoid tissue
Tonsils, spleen, thymus, GALT, BALT, BBB
Increased Th2
Increased IQ
Increased verbal ability
Increased fine motor skill
Relative increased muscle tone
Left post compartment above T6
Decreased tone left ant. compartment below T6
Perseverative
Increased obsession
Increased motor activity
Impulsivity
Increased rt. hemifield awareness
Increased responsiveness/ production
Dopamine/Acetylcholine
Autonomic, immune regulation
Sympathetic/Parasympathetic
Enteric

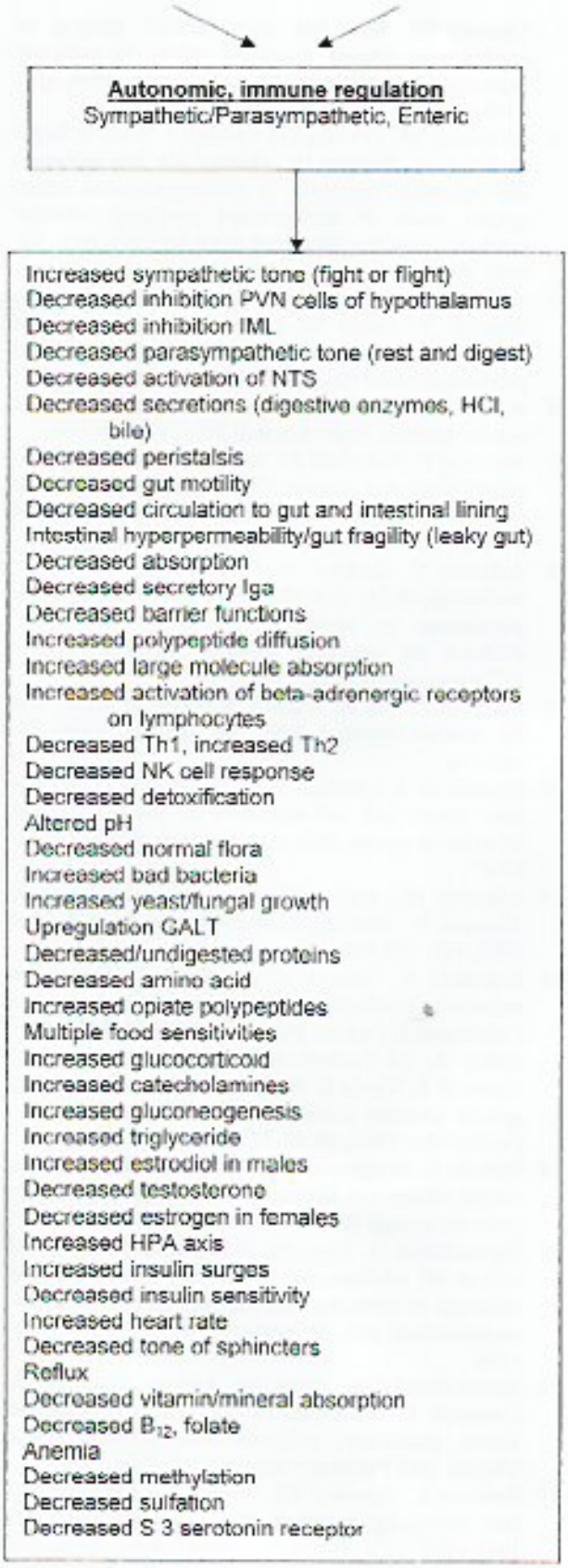


Fig. 2: Right hemisphere model of autism, ADHD, and Asperger's syndrome

Therefore we think that in the case of autism spectrum disorder including ADHD, that somatosensory stimulation will be most effective when the stimulus is applied unilaterally directed toward the underactive right hemisphere.

Employing somatosensory receptors as a way of increasing thalamocortical oscillation rate may be a very useful way of specifically 'speeding up' the underactive hemisphere. By increasing the frequency of the stimulus, we could theoretically achieve an increase in the firing rate of receptors and the pathways that transmit this information to the thalamus and subsequently the brain. Somatosensory stimulation that increases the function and flow of afferent information to the cerebellum could increase its activity to the VA/VL nuclei in the thalamus. This hypothesized increased oscillation of the VA/VL may then, through entrainment, increase the oscillatory rate of the non-specific intralaminar nucleus, which would increase the firing rate of the entire hemisphere.

We propose that increasing the baseline oscillation speed of one entire hemisphere will enhance the coordination and coherence between the two hemispheres allowing for enhanced motor and cognitive binding. This would also allow sensory and motor functions to summate more efficiently leading to improved sensory perception, increased motor coordination and reduced reaction time. Utilizing specific forms of sensory and motor stimulation and/or cognitive stimuli targeted to both specific and non-specific circuits may enhance this effect. Therefore a multimodal approach would utilize a combination of sensory, motor and specific cognitive activities all directed specifically to one hemisphere based on the individual functional needs of the individual child.

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Towards an Effective Definition of Death and Disorders of Consciousness

Calixto Machado[1] and Gerry Leisman[2,3]

[1]*Institute of Neurology and Neurosurgery, Havana, Cuba,*
[2]*F.R. Carrick Institute for Clinical Ergonomics, Rehabilitation, and Applied Neurosciences, Leeds Metropolitan University, Leeds, UK and* [3]*University of Haifa, Israel*

SYNOPSIS

There exists much controversy in providing an effective definition of human death, largely due to the lack of a rigorous separation and ordered formulation of three distinct elements: a universally accepted definition of death, the medical criterion (anatomical substrata) for determining that death has occurred, and the tests to prove that the criterion has been satisfied. The papers herein review medical standards, philosophical arguments, neurophysiological knowledge, behavioural and cognitive theory and the legal ramifications of the brain-oriented standards of death (whole brain, brainstem and higher brain). The papers examine the notion of connectivities and networks of conscious experience in order to formulate an effective definition of death, based on the basic physiopathological mechanisms of consciousness. We cannot simply differentiate and locate arousal as a function of the ascending reticular activating system, and awareness as a function of the cerebral cortex. Substantial interconnections among the brainstem, subcortical structures, and the neocortex are essential integrating components of human consciousness. This paper attempts to reconcile the brain-oriented standards that are currently inconsistent. The thread of the arguments is the basis for a standard of human death that includes consciousness as the most important function of the body, because it provides the capacity for integrating the functions of the body. The notion of consciousness as the ultimate integrative function is more consistent with the biologically-based systems than the more philosophically-based notions of personhood. Both sides of the argument are presented herein.

KEY WORDS

consciousness, death, arousal, functional disconnection, integrative function

Address for Correspondence:
Prof. Gerry Leisman
16 Cortelyou Road
Merrick, NY 11566, USA
e-mail: drgersh@yahoo.com

Dr. Calixto Machado
Institute of Neurology and Neurosurgery
Apartado Postal 4268
Ciudad de La Habana 10400, Cuba
e-mail: braind@infomed.sld.cu

Long ago, well before the introduction of modern life-sustaining technology, all agreed that death occurred when heartbeat and breathing ceased, and the soul abandoned the body. Nonetheless, the concept of death evolved as technology progressed, forcing medicine and society to redefine the ancient cardio-respiratory diagnosis to a neurocentric diagnosis of death /10,13-15,17, 23,25,26/. This was documented by French neurologists and neurophysiologists at the end of the 1950s /24,31/. The result would be a dead brain in a viable body. Is such a 'preparation' alive or dead? /23/.

The end of the 1960s was also prominent for further advances in this area. The Ad Hoc Committee of Harvard Medical School proposed a new criterion of death on neurological grounds /7/. Harvard's report appeared some months after Christian Barnard's first transplantation of a human

heart in December of 1967 /1/.

It is commonly believed that the first set of criteria for brain death (BD) originated in 1968, with the report issued by the Ad Hoc Committee of the Harvard Medical School. Actually, five years before the Harvard criteria appeared, Guy Alexandre, a Belgian surgeon at the Catholic University of Louvain, introduced a set of BD criteria based on the description of coma dépassé, and carried out the first transplant in his country /19/.

The year of 1981 was highlighted by the report of the President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research to define death /30/. This radically changed the course of the debate about human death, marking a turning point when brain-oriented definitions of death started to be formulated, and brain death (BD) was gradually accepted as the death of the individual /10,13-15,17,23,25,26/.

Three main brain-oriented formulations of death have been described historically: *whole brain*, *brainstem* and *higher brain* standards /4,10,16/. Most authors generally agree with the whole brain view, proposing that BD is the irreversible loss of all brain functions /2-4/. The brainstem standard was adopted in several Commonwealth countries. This view has been powerfully articulated by Christopher Pallis, who emphasized that the capacity for consciousness and respiration are two hallmarks of life of the human being, and that brainstem death predicts an inescapable asystole /25,26/. The higher brain formulation springs largely from consideration of the persistent vegetative state (PVS), and has been mainly defended by philosophers. The higher brain theorists have defined human death as the 'the loss of consciousness' (*definition*), related to the irreversible destruction of the neocortex (*anatomical substratum*), suggesting, inappropriately, that those patients in PVS, or with severe cerebral malformations, can be diagnosed as dead /32,33/.

Plum and Posner proposed that consciousness is "the state of awareness of self and the environment" /28,29/. According to these authors, consciousness has two physiological components: arousal and awareness. Although arousal is mainly related to the functioning of the ascending reticular system located in the brainstem and diencephalon, and awareness to the cerebral cortex function, consciousness does not bear a simple one-to-one relationship with higher or lower brain structures, because the physical substratum for consciousness is based on anatomy and physiology throughout the brain /6,8,9,12,13,16,27-29/. Ultimately, the brainstem controls brain function and is responsible for regulating in part breathing, heart rate, and reflexes such as gagging or coughing when the airway is obstructed, withdrawal from pain, and pupillary function /2,5/. Examples are presented in the papers that follow of a rooster having 'lived' with only an intact brainstem, after decapitation, for as long as 18 months. We also see examples in the Soviet reanimation studies of the 1930s and 1940s that allow us to question the nature of being alive.

There is a large proportion of societies and cultures that distinguish between social personhood and physical existence. In many cultures persons with particular diseases and disabilities have been treated as 'socially dead' before physical death had occurred. Social death has been used as a means of dealing with newborns with anomalies and disabilities, with the elderly infirm, and as punishment. Corpses are treated in some societies as being inhabited by the vital principle for long after we would declare death, as for instance among the Tibetans who continue to chant verses to the body and its listening spirit for one week after respiration has stopped. And many societies invest greater or lesser faith in the continued presence of the dead as members of the social order, with rights and obligations. Conversely, birth is not the universally recognized beginning of social life. In some societies infants were not considered persons until one year of age /6,27/.

However, it is commonly believed that the concept of BD evolved to benefit organ transplantation. A historical analysis of the literature reveals that both brain death and transplantation had fully separate origins. Organ transplantation became possible with technical advances in surgery and immunosuppressive treatment. The concept of BD evolved with the introduction of intensive care units /20,21/.

Moreover, well known cases such as those of

Terry Schiavo and others including Karen Ann Quinlan and Nancy Cruzan in the USA, and Tony Bland in the UK, raised new controversies about the diagnosis and management of PVS and the minimally conscious state (MCS), with powerful ethical and legal debates about diagnosing these patients as dead, stopping fluids and nutrition, keeping the patients alive, or attempting to rehabilitate them from the these clinical 'altered states' of consciousness /22,23/.

Since 1992, we have held the International Symposia on Coma and Death in Havana (1992, 1996, 2000, 2004) /18/. On May 20-23, 2008 we held the 5th International Symposium of the Definition of Death Network in Varadero Beach, Cuba, to discuss issues related to human death and disorders of consciousness. This special issue of **Reviews in the Neurosciences** collects the most important papers presented at that Conference for reflection, theory development, and clinical practice effecting better living and more dignified and honourable dying.

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