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

[1, 2]University of Haifa, Mt. Carmel, Haifa, Israel 31905

E-mail: g.leisman@alumni.manchester.ac.uk

Abstract

We outline in this paper 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.

INTRODUCTION

Epigenetic Effects on Autistic Spectrum Disorders

Neurobehavioral disorders of childhood that include 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 US /121/, has recently been estimated to have a prevalence of 1 in 150 in the United States /121, 123/. In the UK recent estimates have reported a prevalence of autism in 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 alarmingly increasing. A recent study in Denmark /11/ has shown that ADHD, Tourette's syndrome and 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 was 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 percent between monozygotic (identical) twins compared to less than 5 percent 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 behavioural 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 and epigenetic phenomena rather than genetic and epigenetic factors can also be passed on to offspring with out altering DNA through various mechanisms that affect genetic expressions 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/ provide an explanation that, "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* (or 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 being "recovered" are more common and documented. 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 /131,22,33,104-106/. Autism rate increases imply non-inevitable factors (i.e. environmental factors and gene-environment interactions with resultant non-inevitable alterations in metabolism, gene expression, signalling etc., some of which may be treatable and reversible. According to Herbert /64/, she proposes a more conservative description of autism, as a behavioural syndrome with a biological basis and systemic features, influenced by genes and gene-environment interactions. The proposed shifts, from "brain based" to "systemic-genetic" aetiology are 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 behavioural 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 like 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 velocities, 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. Questions about 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 etc. are coincidental or a core part of the condition? Whether (and if so in what ways) it is 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 of strength and weaknesses. 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 weakness. On the other hand other factors that have been looked at as causative factors, like inflammation, and white matter growth, don't seem to show this type of relationship. They seem to be nonspecific 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 be associated with networks with reduced coherence.

Associated with these functional asymmetries or imbalances also seem to be associated 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 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 attention-deficit/hyperactivity disorder (ADHD) /46/, autism /118/, bipolar disorder (especially its manic phase) /3/, obsessive-compulsive disorder   (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 co-morbidity /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 behaviours, 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 pathoaetiology of a variety of neurodevelopment 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 autism's definition.

MOTOR AND SENSORY FUNCTION IN AUTISTIC SPECTRUM DISORDERS

Problems of Inter-hemispheric Interaction

In general, dopaminergic systems (DA) tend to be more involved in motor than in sensory behaviour, 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'') behaviour. As a corollary to its role in distally oriented, sequential voluntary motivational behaviours, 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 behaviours 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 of reduced social ability, nonverbal communication, Hyperactivity, perseverative behaviour 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 a 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. Autistics 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 inter-hemispheric communication /80,81,83,92/.

Sensory Motor Interaction: Global v. 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 which 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 vs. sensory feedback. Another equally important dimension in the understanding of the

organisation 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 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 and Mishkin's "what" vs. "where" distinction with a distinction between "what" vs. "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 where there exists a 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. ASD individuals show a bias, for part over wholes - 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 autistic individuals along with sensory motor deficits explained partly by a more ventrally based sensory motor system focusing more on action and less on perception. Autistics are believed to have poor body schema and spatial localization of body parts. Many autistics 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 the vision and audition with the emphasis on the ventral system and decrease in the dorsal system.

The mirror neuron system is dysfunctional in autistics /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 autistics 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 being 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 multi-modal 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 over-active 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 behaviour 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 over-activation 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 over-activation of DA systems represents the most characteristic brain dysfunction in autism. They are: (1) the link between hyperdopaminergic activity and the various behaviours 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 Martha 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."

Thee exists a high comorbidity of many neurobehavioral disorders /159/, such as the case with disorders like ADHD and schizophrenia, OCD, and Tourette's. The most likely cause of this disruptive coordination is a dysfunction 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 feed forward, 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 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. That theory is that lack of synchronization or a temporal coherence between two hemispheres and/or various large areas of central nervous system leads to a lack of optimised communication between these areas. This lack of optimised activity leads to an under connectivity 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 of 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/, 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 below and serves as a comparison point for a discussion of functional disconnectivities and synchronous gamma band activity in autistic spectrum disorders.

<div align="center">INSERT FIGURE 1 ABOUT HERE</div>

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, autistic spectrum individuals seems 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 right hemisphere   is

involved in global processing. Social comprehension involves empathy for others' experiences and appropriate responses to nonverbal cues. Previous research using magnetic resonance imaging (MRI) has suggested a relationship between brain morphology and psychiatric syndromes, such as attention-deficit hyperactivity disorder (ADHD) that typically entails 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/ fifty-nine 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 in with attention-deficit disorder with but without hyperactivity, most evidence supports the view that right-hemispheric-type activity, relying more on 5-HT and 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 behaviour 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., humour 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 /62,90,91,111,132,118/.

Studies /62,111,156/ have also shown that in ADHD and in autism individuals often show deficient right hemisphere abilities that seem to resemble individuals 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 nonretarded autistic adults, and to age and intelligence-matched controls. Autistic subjects performed significantly less well than controls on all measures, replicating 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 behaviours 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 autistic individuals primarily lack mind reading capacities or the ability to non-verbally communicate 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 related especially to emotion. All of these abilities are well recognized to be right hemisphere based. Most evidence supports the view that right-hemispheric-type activity, relying more on 5-HT and NE transmission, is relatively deficient in autism, thereby shifting the neurochemical balance even more toward the DA-rich left hemisphere /117/.

For example, deficiencies in social and emotional behavior that follow damage to the right hemisphere /55,65/ are very similar to those in autism. Several abnormalities found in autism, deficient *theory of mind*, impaired processing of facial expression, deficient prosody, impaired judgment of speaker intent (e.g., humour 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 /62,91,111,132,152/. However, we will also see that when one hemisphere is suppressed or inhibited the other hemispheres abilities may become enhanced. This may be an explanation for savant syndrome in which most of the exceptional abilities seem to be left hemisphere in nature. Math calculation, fine motor skill, imitation, musical playing and memorization abilities, hyperlexia, visual imagery, and puzzle ability etc. The level of increase in left hemisphere skills seems to be negatively correlated with decreases in right hemisphere skills. Research has shown that employing transcranial magnetic electrical stimulation demonstrates 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 dysfunction 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 & 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 the 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 for example /17/, twenty-one 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 with 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, 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 autistic spectrum individuals appear to be overly sensitive and prone to autoimmune regulated disorders. They seem to have poor detoxification profiles that seem to be related to the poor digestion and autoimmunity /47/. Additional symptoms as indicated earlier in the paper include poor socialization, nonverbal communication, poor empathy, poor gross motor development and low muscle tone, poor gross spatial awareness, incoordination, abnormal gait and posture, poor attention, and impulse control, enhanced local processing of visual and auditory input and reduced global processing of both.

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 /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 contain visceral homunculi. The second source of interoceptive maps consist of different classes of receptors found on the body's surface and include the teeth, gums, and tongue. These receptors carry information about "homeostatic" condition of the body including, temperatures, pain, itch, 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 left and right insula, only the human brain performs an additional level of integration. The information from both your insula 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 Behaviour, 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 anterior cingulate cortex (ACC) and fronto-insula (FI) cortex. Unlike most neuron types, the 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 nonverbal 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 FI and ACC.

Functional magnetic resonance imaging studies indicate that 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 of yet, we do not know the mechanisms responsible for the differentiation of the complex social emotions that activate 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 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 reaction" reactions and feelings that form the foundation of intuition.

Right Hemisphere Dysfunction and Immunity

The connection with the right hemisphere and the immune system has also been well documented in the literature. The right hemispheres role in regard to the immune system is immunosuppressive /cf. 22/. It has been shown that with lesions to the right frontal areas, there is a significant increase in the production of lymphoid tissue as well as an increase production and reaction of IgE and IgG cells, T-cells, and increased production 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 hemispheres control of the immune system. Lastly, with regard to many of the 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 bowl 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 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 below.

INSERT FIGURE 2 ABOUT HERE

DISCUSSION

Many recent reports /12,67,153/ has generated a vibrant discussion that is still ongoing in print that autistic spectrum children excrete significantly high levels of urinary *methylmalonic acid* excretion as compared to age-matched controls, clearly an indication of a functional vitamin B12 deficiency. A raised *methylmalonic* secretion is often coupled with elevated *homocysteine*, the metabolic abnormalities associated with functional B12, folate, and/or B6 deficiency. Elevated urinary *methylmalonic acid* could represent a functional B12 deficiency, which may track back to certain biochemical genetic markers. In other words, autistic spectrum children may have an epigenetic susceptibility for altered vitamin B12-dependent metabolism. Alternatively, they may be manifesting a malabsorption disorder, such as a parietal cell insufficiency of intrinsic factor secretion. Vitamin B12 is a large nutrient that needs to be absorbed in the absence of a "helper," or

intrinsic factor. This raises all sorts of questions about gastrointestinal (GI) physiology, vitamin B12 absorption, and the effect B12 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 the 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 include a multimodal therapeutic approach that would include a combination of somatosensory, cognitive, behavioural and biochemical, 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 autistic spectrum disorder including ADHD resembles individuals with right hemisphere damage and neglect, that somatosensory stimulation may be a useful treatment in these disorders. The research on somatosensory stimulation and neglect /106/ has shown that various modalities such as TENS, vestibular, optokinetic, vibration, and tactile stimulation can all reduce the 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 the brain lesion 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 it 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 the 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. 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 under active right hemisphere.

Employing somatosensory receptors as a way of increasing thalamocortical oscillation rate may be a very useful way of specifically "speeding up" the under active 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 will also allow sensory and motor functions to summate more efficiently leading to improved sensory perception and increase motor coordination and reduced reaction time. Utilizing specific forms of sensory, motor may enhance this effect, and/or cognitive stimuli target to both specific and non-specific circuits. Therefore a multimodal approach utilizing 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.

REFERENCES

1 Adler, P., McDonough-Ryan, K. W., Sax, S. K., Holland, S., Arndt, S. M., and Strakowski. (2000) FMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive-compulsive disorder. *J. Psychiatry Res.* **34,** 317–324.

2 Allman, J. M, Watson, K. K., Tetreault, N. A., and Hakeem, A. Y. (2005) Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn. Sci*. **9(8)**, 367-373.

3 Anand, A. Verhoeff, P., Seneca, N., Zoghbi, S.S., Seibyl, J.P. Charney, D.S., and Innis, R.B. (2000) Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am. J. Psychiatry* **157,** 1108-1114.

4 . Andreasen, N. C., O'Leary, D. S. Cizadlo, T., Arndt, S. Rezai, K., Ponto, L. L., Watkins, G. L., and Hichwa, R. D. (1996) Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proceedings of the National Academy of Sciences of the U S A*. **93,** 9985-9990.

5 Andreasen, N. C. Nopoulos, P., O'Leary, D. S., Miller, D. D., Wassink, T., and Flaum M. (1999) Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biol. Psychiatry* **46,** 908-920.

6 Andres C. (2002) Molecular genetics and animal models in autistic disorder. Brain Res. Bull. **57**, 109–19.

7 Ashwood, P., and Wakefield, A.J. (2006) Immune activation of peripheral blood and mucosal CD3+ lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms. *J. Neuroimmunol*. **173(1-2)**, 126-34.

8 Ashwood, P., Anthony, A., Pellicer, A. A., Torrente, F., Walker-Smith, J. A., and Wakefield, A.J. (2003). Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J. Clin. Immunol*. **23**, 504-517.

9 Ashwood, P., and Van de Water, J (2004). A review of autism and the immune response. *Clin. Develop. Immunol*. **11**, 165-174.

10 Bachevalier, J. and Loveland, K. A. (2006) The orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism. *Neuroscience Biobehav. Rev.* **30**, 97–117.

11 Atladóttir, H.O., Parner, E. T., Schendel, D., Dalsgaard, S., Thomsen, P., and Thorsen, P. (2007) Arch. Pediatr. Adolesc. Med. **161(2)**, 193-198

12 Baghdadli, A., Gonnier, V., and Aussilloux, C. (2002) Revue des traitements psychopharmacologiques de l'autisme chez l'adolescent et l'adulte *Encephale* **28(3,pt. 1)**, 248-254.

13 Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., and Rutter, M. (1995) Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol. Med*. **25**, 63–77.

14 Barbeau A. (1984) Manganese and extrapyramidal disorders (a critical review and tribute to Dr. George C. Cotzias). *Neurotoxicol.* **5,** 13-35.

15 Barkhudaryan N, Dunn AJ (1999). Molecular mechanisms of actions of interleukin-6 on the brain, with special reference to serotonin and the hypothalamo-pituitary-adrenocortical axis. Neurochem Res. **24(9)**:1169-80

16 Barnea-Goraly, N., Kwon, H. Menon, V. Eliez, S. Lotspeich, L. and Reiss, A.L. (2004) White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biological Psychiatry* **55,** 323-326.

17 Bennetto, L., Kuschner, E. S., and Hyman, S. L. (2007) Olfaction and taste processing in autism. *Biol. Psychiatry* **62(9)**, 1015-1021.

18 Berardelli, A., Curra, A., Fabbrini, G., Gilio, F., and Manfredi, M. (2003) Pathophysiology of tics and Tourette's syndrome. *J. Neurology* **250**, 781–787.

19 Berthoz, S., Armony, J. L., Blair, R. J., and Dolan, R. J. (2002) An fMRI study of intentional and unintentional (embarrassing) violations of social norms. *Brain* **125(8)**, 1696-1708.

20 Bishop, D. V. (1989) Autism, Asperger's syndrome and semantic-pragmatic disorder: where are the boundaries? *Br. J. Disord. Commun*. **24(2)**, 107-121.

21 Bejerot, S., Nylander, L., and Lindström. E. (2001) Autistic traits in obsessive-compulsive disorder. *Nord. J. Psychiatry* **55(3)**,169-76.

22 Blaxill, M. F., Baskin, D. S., Spitzer, W. O. (2003) Commentary: Blaxill, Baskin, and Spitzer on Croen et al. (2002), the changing prevalence of autism in California. *J. Autism Dev. Disord.* 33(2), 223-226; discussion 227-229.

23 Blumberg, H.P., Stern, E., Martinez, D., Ricketts, S., de Asis, J., (2000) Increased anterior cingulate and caudate activity in bipolar mania. *Biol. Psychiatry* **148**, 1045–1052.

24 Boddaert, N. and Zilbovicius, M. (2002) Functional neuroimaging and childhood autism. *Pediat. Radiol.* **32**, 1-7.

25 Brambilla, F., Bellodi , L. Perna, G. Arancio C., and Bertani, A. (2000) Dopamine function in obsessive—compulsive disorder: Growth hormone response to apomorphine stimulation. *Biol. Psychiatry* **42**, 889 – 897.

26 Brandt, Th., Dieterich, M., and Danek, A. (1994) Vestibular cortex lesions affect the perception of verticality *Ann. Neurol.* **35: 4**, 403-412.

27 Braun, A. R., Stoetter, B., Randolph, C., Hsiao, J. K.,Vladar, K., Gernert, J., Carson, R. E., Herscovitch, P., and Chase, T. N. (1993) The functional neuroanatomy of Tourette's Syndrome: an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. *Neuropsychopharmacol.* **9**, 277–291.

28 Braun, C. M. Larocque, C. Daigneault, S., and Montour-Proulx, I. (1999). Mania, pseudomania, depression, and pseudodepression resulting from focal unilateral cortical lesions. *NeuroPsychiatry Neuropsychol. Behav. Neurol.,* **12**, 35–51.

29 Chugani, H. T., Müller, R. A., and Chugani, D. C. (1996) Functional brain reorganization in children. *Brain Develop.* **18**, 347-356.

30 Critchley, H. D., Corfield, D. R., Chandler, M. P., Mathias, C. J., and Dolan, R. J. (2000) Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol*. **15(523, Pt 1)**, 259-270.

31 Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B. K., Cipolotti, L., Shallice, T., and Dolan, R. J. (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* **126(Pt 10)**, 2139-2152.

32 Critchley HD, Rotshtein P, Nagai Y, O'Doherty J, Mathias CJ, and Dolan RJ. (2005) Activity in the human brain predicting differential heart rate responses to emotional facial expressions. *Neuroimage* **24(3)**, 751-62.

33 Croen, L..A., Grether, J. K., Hoogstrate, J., and Selvin, S. (2002), The changing prevalence of autism in California. *J. Autism Dev. Disord*. **32(3),** 207-215.

34 Coco, M. L., and Weiss, J. M. (2005) Neural substrates of coping behavior in the rat: possible importance of mesocorticolimbic dopamine system. *Behav. Neurosci*. **119**, 429–451.

35 Cools, R. (2008) Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist*. **14,** 381-395.

36 Cummings. J. L. (1997) Neuropsychiatric manifestations of right hemisphere lesions. *Brain Lang.* **5,** 22–37.

37 Dalton, P., Deacon, R., Blamire, A., Pike, M., McKinlay, I., Stein, J., Styles, P., and Vincent, A. (2003) Maternal neuronal antibodies associated with autism and a language disorder. *Ann. Neurol*. **53(4)**, 533-7.

38 Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci*. **351(1346),** 1413-1420.

39 DeBrabander, B., and DeClerck, C. (2004) A possible role of central dopamine metabolism in individual differences in locus of control. *J. Personality Individ. Differ.* **37,** 735–750.

40 Delaveau, P., Salgado-Pineda, P., Wicker, B., Micallef-Roll, J., and Blin, O. (2005) Effect of levodopa on healthy volunteers' facial emotion perception. *Clin. Neuropharmacol*. **28,** 255–261.

41 DelParigi, A., Chen, K., Salbe, A. D., O'Hill, J., Wing, R. R., Reiman, E. M., and Tataranni, P. A. (2004) Persistence of abnormal neural responses to a meal in postobese individuals *Int. J. Obesity* **28,** 370–377.

42 DePue, R.A., and Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav. Brain Sci.* **22,** 491–569.

43 Diamond, A., Prevor, M. B., Callender, G., Druin, D. P. (1997). Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monogr. Soc. Social Res. Child Devel.* **162,** 1–208.

44 Dijkerman, H. C., and de Haan,E. H. F. (2007) Somatosensory processes subserving perception and action. *Behav. Brain Sci.* 30(2), 189-201.

45 Djordjevic, J., Zatorre, R. J., Petrides, M., Boyle, J. A. and Jones-Gotman, M., (2005) Functional neuroimaging of odor imagery. *Neuroimage* **24(3)**, 791-801.

46 Drtilkova, I. Sery, O. Theiner, P. Uhrova, A. Zackova, M., Balastikova, B. and Znojil, V. (2008) Clinical and molecular-genetic markers of ADHD in children. *Neuro Endocrinology Letters* **29,** 320-327.

47 Edelson, S. B., and Cantor, D.S. (1998) Autism: xenobiotic influences. *Toxicol. Ind. Health.* **14(4)** ,553-563.

48 Egeth, M., and Kurzban, R. (2008) Representing metarepresentations: Is there Theory of Mind-specific cognition? *Consciousness Cognit.* **18,** Eprint

49 Fitzgerald, P. B., Brown, T. L. and Daskalakis, Z. J. (2002) The application of transcranial magnetic stimulation in psychiatry and neurosciences research *Acta Psychiatry Scand.* 105(5), 324-340.

50 Flor-Henry, P. (1986) Observations, reflections and speculations on the cerebral determinants of mood and on the bilaterally asymmetrical distributions of the major neurotransmitter systems. *Acta Neurol. Scand.* **74**, 75–89.

51 Frith, U. (1996) Cognitive explanations of autism. *Acta Paediatrica*, Supplement. 416, 63-68.

52 Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A., Davies, S. E., Berelowitz, M., Forbes, A., Wakefield, A. J., Walker-Smith, J. A., and Murch, S. H.Colonic (2001) CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J. Pediatr*. **138(3)**, 366-372.

53 Gillberg, C., Rosenhall, U., and Johansson, E. (1983) Auditory brainstem responses in childhood psychosis. *J. Autism Development. Disord.* **13,** 181–195.

54 Gillberg, C., and Billstedt, E. (2000) Autism and Asperger syndrome: coexistence with other clinical disorders. Acta Psychiatry Scand. 102, 321–330.

55 Goldberg, T. E., Maltz, A., Bow, J. N., Karson, C. N., and Leleszi, J.P. (1987) Blink rate abnormalities in autistic and mentally retarded children: relationship to dopaminergic activity. *J. Am. Acad. Child. Psy.* **26** ,336–338.

56 Goldstein S. and Schwebach, O. J. (2004). The comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: results of a retrospective chart review. *J. Autism Dev. Disord*. **34(3)**, 329-39.

57 Goodale, M. A., and Milner, A. D. (1992) Separate visual pathways for perception and action. *Trends Neurosci.,* **15***,* 20-25.

58 Grandin, T. (2008) *The way I see it*. Arlington, TX, New Horizons.

59 Gur, R. E., and Chin. S. (1999) Laterality in functional imaging studies of schizophrenia. *Schizophrenia Bulleten* **25,** 141–156.

60 Hadjikhani, N. Joseph, R. M., Snyder, J. and Tager-Flusberg, H. (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. *Cerebral Cortex*. **16(9)**, 1276-1282

61 Hains, A.B., and Arnsten, A.F. (2008). Molecular mechanisms of stress-induced prefrontal cortical impairment: implications for mental illness. *Learn. Memory* **15,** 551-564.

62 Happé, F., Brownell, H., and Winner, E. (1999). Acquired 'theory of mind' impairments following stroke. *Cognition*. **70(3)**, 211-40.

63 Harper, LV. (2005) Epigenetic inheritance and the intergenerational transfer of experience. *Psychol. Bull*. **131**, 340–60.

64 Herbert, M.R. (2005) A brain disorder or a disorder that affects the brain? *Clin. NeuroPsychiatry* **2**, 354-379.

65 Herbert, M.R., Ziegler, D.A., Makris, N., Filipek, P.A., Kemper, T.L., Normandin, J.J., Sanders, H.A., Kennedy, D.N., and Caviness Jr., V. S. (2004) Localization of white matter volume increase in autism and developmental language disorder. *Ann. Neurol.* **55**, 530-540.

66 Herrmann,C. S.,and Mecklinger, A. (2000) Magnetoencephalographic responses to illusory figures: early evoked gamma is affected by processing of stimulus features. *Int. J. Psychophysiol*. **38(3)**, 265-281.

67 Herrmann, W. And Obeid, R. (2007) Biomarkers of folate and vitamin B(12) status in cerebrospinal fluid. *Clin. Chem. Lab. Med*. **45(12)** ,1614-1620.

68 Jass, J. R. (2005) The intestinal lesion of autistic spectrum disorder. Eur   J *Gastroenterol. Hepatol*. **17(8)**, 821-822.

69 Joblanka, E., and Lamb, M. J. (2002) The changing concept of epigenetics. *Ann NY Acad Sci.* **981**, 82-96.

70 Johnson, S. C. (2003) Detecting agents. *Philos. Trans. R. Soc. Lond. B Biol. Sci*. 358(1431), 549-59.

71 Jones, J. R., Skinner, C., Friez, M. J., Schwartz, C. E., and Stevenson, R.E. (2008) Hypothesis: dysregulation of methylation of brain-expressed genes on the X chromosome and autism spectrum disorders. ***Am. J. Med. Genet. A***. 146A(17), 2213-2220.

72 Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., and Just, M. A. (2008) Atypical frontal-posterior synchronization of Theory of Mind regions in autism during mental state attribution. *Social Neurosci.* **3**, 1-18.

73 Kano, Y., Ohta, M., Nagai, Y., Pauls, D. L., Leckman, J. F. (2004) Obsessive-compulsive symptoms in parents of Tourette syndrome probands and autism spectrum disorder probands. *Psychiatry Clin. Neurosci*. **58(4)**, 348-52

74 Kjelgaard, M. M. and Tager-Flusberg H. (2001) An Investigation of Language Impairment in Autism: Implications for Genetic Subgroups. *Lang Cogn Process*. 16(2-3): 287–308.

75 Koch, P., and Leisman, G. (1996) Wave theory of large-scale organization of cortical activity. *Int. J. Neurosci.* **86,** 179-196.

76 Lachaux, J.P., Jung, J., Mainy, N., Dreher, J.C., Bertrand, O., Baciu, M., Minotti, L., Hoffmann, D., and Kahane, P. (2008) Silence is golden: transient neural deactivation in the prefrontal cortex during attentive reading. *Cereb Cortex*. **18(2),** 443-50.

77 La Malfa, G., Lassi, S., Bertelli, M., Salvini, R., and Placidi, G. F. (2004) Autism and intellectual disability: a study of prevalence on a sample of the Italian population. *J. Intellect. Disabil. Res*. **48(Pt 3)** , 262-7

78 Landvogt, E., Mengel, P., Bartenstein, H.G., Buchholz, M., Schreckenberger, T., Siessmeier, A., Scheurich, R., Feldmann, J., Weglage, P., Cumming, F., Zepp, K., Ullrich. Reduced cerebral fluoro-L-dopamine uptake in adult patients suffering from phenylketonuria. *J. Cereb. Blood Flow Metabol.* **28,** 824-831.

79 Leisman. G. (1976) "The role of visual processes in attention and its disorders." In: G. Leisman (Ed.) *Basic Visual Processes and Learning Disability*. Springfield, IL, Charles C. Thomas, pp. 7-123.

80 Leisman, G. and Ashkenazi, M. (1980) Aetiological factors in dyslexia: IV. Cerebral hemispheres are functionally equivalent. *Int. J. Neurosci.* **11**, 15-164.

81 Leisman, G. (2002) Coherence of hemispheric function in developmental dyslexia. *Brain Cognit.* **48,** 425-431.

82 Leisman, G. and Zenhausern, R. (1982) "Integratory systems deficits in developmental dyslexia." In: R.N. Malatesha, L. Hartlage (Eds.) *Neuropsychology and Cognition* Elsevier, Amsterdam, The Netherlands, pp. 281-309.

83 Leisman, G. and Melillo R.M (2004) Functional Brain Organization In Developmental Dyslexia. In: H. D. Tobias (Ed.) *Focus on Dyslexia Research*. Nova, Hauppauge, NY, pp.105-149.

84 Leisman, G. and Melillo, R. M. (2006) "Cortical asymmetry and learning efficiency: A direction for the rehabilitation process". In: S. V. Randall (Ed.) *Learning Disabilities: New Research*. Nova, Hauppauge, NY: Nova, pp. 1-24.

85 Leisman, G. and Melillo, R.M. (2009) Functional disconnectivities in autism. *J. Disab. Hum. Develop.* 2009 (In press)

86 Lelord, G. Hérault, J., Perrot, A. Hameury, L. Lenoir, P. Adrien, J.L., Mallet, J., and Muh, J.P. (1993). L'autisme de l'enfant : une déficience relationnelle liée à un trouble du développement du système nerveux central. *Bul. Acad. nationale méd..* **177,** 1423-1430; discussion 1430-1432.

87 Lenz, D., Schadow, J., Thaerig, S., Busch, N.A., and Herrmann, C.S. (2007) What's that sound? Matches with auditory long-term memory induce gamma activity in human EEG. *Int. J. Psychophysiol.* **64(1)**, 31-38.

88 Liu, Z., Li, N., and Neu, J. (2005) Tight junctions, leaky intestines, and pediatric diseases. *Acta Paediatr*. **94(4)**,386-393.

89 López, B., Leekam, S. R., and Arts, G. R. (2008) How central is central coherence? Preliminary evidence on the link between conceptual and perceptual processing in children with autism. *Autism* **12**, 159-171.

90 Mandell, A. J. (1980) "Toward a psychobiology of transcendance: god in the brain." In: Davidson JM, Davidson RJ, (Eds). *The psychobiology of consciousness*. New York, Plenum, pp. 379–464.

91 Manjaly, Z. M., Marshall, J. C., Stephan, K. E., Gurd, J. M., Zilles, K., and Fink, G. R. (2003) In search of the hidden: an fMRI study with implications for the study of patients with autism and with acquired brain injury. *Neuroimage* **19,** 674–683.

92 Melillo, R.M., and Leisman, G. (2004) *Neurobehavioral Disorders of Childhood: An Evolutionary Approach.* Kluwer, New York, NY.

93 Miller, S. R., Miller, C.J., Bloom, J.S., Hynd, G.W., and Craggs, J. G. (2006) Right hemisphere brain morphology, attention-deficit hyperactivity disorder (ADHD) subtype, and social comprehension. *J. Child Neurol*. **21(2),** 139-144.

94 Milner, A. D., and Goodale, M.A. (1995) *The Visual brain in action.* Oxford University Press, New York.

95 Minshaw, N. J. Sung, K. Jones, B. L. and Furman, J. M. (2004). Underdevelopment of the postural control system in autism. *Neurology.* **63(11)**, 2056-2061.

96 Mishkin, M., Ungerleider, L. And Macko, K. A. (2001). „Object vision and spatial vision two cortical parthways." In: W. Bechtel, P. Mandik, J. Mundale, and R. S. Stufflebeam (Eds.) *Philosophy and the Neurosciences: A Reader*. Malden, MA, Blackwell, pp.199-208.

97 Mitchell, R. W. (1997) A comparison of the self-awareness and kinesthetic-visual matching theories of self-recognition: autistic children and others. *Ann. New York Acad. Sci.,* **818**, 38-62.

98 Molloy, R., Brownell, H., & Gardner, H. (1990) "Discourse comprehension by right-hemisphere stroke patients. Deficits of prediction and revision." In: L Y. Joanette and H. M. Brownell (Eds.), *Discourse ability and brain damage: Theoretical and empirical perspectives*, New York, Springer-Verlag, pp. 113-130.

99 Mottron, L., Peretz, I., and Menard, E. (2000) Local and global processing of music in high-functioning persons with autism: beyond central coherence? *J.Child Psychol. Psychiatry* **41(8),** 1057-1065.

100 Mountz, J. M., Tolbert, L. C., Lill, D. W., Katholi, C. R., and Liu, H. G. (1995) Functional deficits in autistic disorder: characterization by technetium-99m-HMPAO and SPECT. *J. Nucl. Med.* **36**, 1156-1162.

101 Mulert, C., Leicht, G., Pogarell, O., Mergl, R., Karch, S., Juckel, G., Möller, H. J., Hegerl. U. (2007) Auditory cortex and anterior cingulate cortex sources of the early evoked gamma-band response: relationship to task difficulty and mental effort. *Neuropsychologia*. **45(10)**, 2294-2306.

102 Nakahachi, T., Yamashita, K., Iwase, M., Ishigami, W., Tanaka, Toyonaga, K., Maeda, S., Hirotsune, H., Tei, Y., Yokoi, K., Okajima, S., Shimizu, A., and Takeda, M. (2008) Disturbed holistic processing in autism spectrum disorders verified by two cognitive tasks requiring perception of complex visual stimuli. *Psychiatry Res.* **159**, 330-338.

103 Nebel K, Wiese H, Stude P, de Greiff A, Diener HC, Keidel M. (2005) On the neural basis of focused and divided attention. *Brain Res Cogn Brain Res.* **25(3)**, 760-776.

104 Newschaffer, C.J., Falb, M.D., and Gurney, J.G. (2005) National autism prevalence trends from United States special education data. *Pediatrics* **115**, e277-e282.

105 Morrow, E.M., Yoo, S.Y., Flavell, S.W., Kim, T.K., Lin, Y., Hill, R.S., Mukaddes, N.M,, Balkhy, S., Gascon, G., Hashmi, A. Al-Saad, S., Ware, J., Joseph, R.M.,

Greenblatt, R., Gleason, D., Ertelt, J.A., Apse, K.A., Bodell, A., Partlow, J.N., Barry, B., Yao, H., Markianos, K., Ferland, R.J., Greenberg, M.F., and Walsh, C.A. (2008). Identifying autism loci and genes by tracing recent shared ancestry. *Science* **11:321(5886)**, 208-209.

106 Nico. D. (1999) Effectiveness of sensory stimulation on tactile extinction. *Exp. Brain Res.* **127,** 75-82.

107 Nieoullon, A. Dopamine and the regulation of cognition and attention. (2002) *Prog. Neurobiol.* **67**, 53-83.

108 Nimchinsky, E. A., Gilissen, E., Allman, J. M., Perl, D. P., Erwin, J. M., and Hof, P. R. (1999) A neuronal morphologic type unique to humans and great apes. *Proc. Natl. Acad. Sci.* U.S.A. **96(9)**, 5268-5273.

109 Oberman, L. M., Hubbard, E. M., McCleery, J. P., Altschuler, E. L., Ramachandran, V. S. and Pineda, J. A. (2005) EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Brain Res. Cognit. Brain Res.* **24(2)**, 190-198.

110 Ornitz, E. M. (1983) The functional neuroanatomy of infantile autism. *International J. Neurosci.* **19**, 85–124.

111 Ozonoff, S., and Miller, J.N. (1996) An exploration of right-hemisphere contributions to the pragmatic impairments of autism. *Brain Lang*. **52(3)**, 411-434.

112 Palit, G., Kumar, R., Gupta, M.B., Saxena, R.C., Patnaik, G.K., and Dhawan, B.N. Quantification of behaviour in social colonies of rhesus monkey. *Indian J. Physiol. Pharmacol.* **41,** 219–226.

113 Panksepp, J. (1999) The affiliative playfulness and impulsivity of extraverts may not be dopaminergically mediated. *Behav.Brain Sci.* **22**, 533–534.

114 Paul, R. H., Clark, C. R, Lawrence, J., Goldberg, E., Williams, L. M., Cooper, N., Cohen, R. A., Brickman, A. M., and Gordon, E. (2005) Age-dependent change in

executive function and gamma 40 Hz phase synchrony. *J. Integr. Neurosci*. **4(1),** 63-76.

115 Perry, R. J., Rosen, H. R., Kramer, J. H. Beer, J.S., Levenson, R. L., and Miller, B. L. (2001) Hemispheric dominance for emotions, empathy and social behaviour: evidence from right and left handers with frontotemporal dementia. *Neurocase* **7,** 145–160.

116 Petronis, A. (2001) Human morbid genetics revisited: relevance of epigenetics. *Trends Genet*. 17, 142–147.

117 Previc, F. H. (1996) Nonright-handedness, central nervous system and related pathology, and its lateralization: a reformulation and synthesis. Develop. Neuropsychol. **12**, 443–515.

118 Previc, F.H. (1999) Dopamine and the origins of human intelligence. *Brain Cognit*. **41**, 299–350.

119 Previc, F. H. (2004) "An integrated neurochemical perspective on human performance measurement." In: J.W. Ness, V. Tepe, D. R. Ritzer (Eds.) *The Science and Simulation of Human Performance*. Elsevier, Amsterdam, The Netherlands, pp. 327–90.

120 Previc, F.H. (2006) The role of the extrapersonal brain systems in religious behavior. *Conscious Cogn.* **15**, 500–539.

121 Previc F. H. (2007) Prenatal influences on brain dopamine and their relevance to the rising incidence of autism *Med. Hypotheses* **68(1)**, 46–60.

122 Pritchard, T. C., Macaluso, D. A., and Eslinger, P. J. (1999) Taste perception in patients with insular cortex lesions. *Behav. Neurosci*. **113(4)**, 663-671.

123 Ray-Mihm, R. (2008) Autism: part I. deficits, prevalence, symptoms, and environmental factors. *J. Contin. Educ. Nurs.* **39(2)**, 55-56.

124 Ridley, R. M., and Baker, H. F. (1982) Stereotypy in monkeys and humans. *Psychol. Med.* **12**, 61–72.

125 Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S., and Romano, J. (1996) Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *J. Comp. Neurol.* **370**, 247–261.

126 Robertson, M. A., Sigalet, D. L., Holst, J. J., Meddings, J. B., Wood, J., and Sharkey, K. A. (2008) Intestinal permeability and glucagon-like peptide-2 in children with autism: a controlled pilot study. *J. Autism Dev. Disord*. **38(6),** 1066-71.

127 Robertson, M.M. (2003) Diagnosing Tourette syndrome: is it a common disorder? *J. Psychosom. Res.* **55,** 3–6.

128 Robison, L.M., Skaer, T.L., Sclar, D.S., and Galin, R.S. (2002).. Is attention deficit hyperactivity disorder increasing among girls in the US? Trends in diagnosis and the prescribing of stimulants. *CNS Drugs* **16,** 129–137.

129 Rotenberg, V. S. (1994) An integrative psychophysiological approach to brain hemisphere functions in schizophrenia. *Neurosci. Biobehav. Rev.* **18**, 487–495.

130 Rumsey, J. M., and Hanahan, A. P. (1990) Getting it 'right': performance *of high-functioning autistic adults on a right-hemisphere battery*.J. Clin. Exp. Neuropsychol*. **12**, 81.

131 Rutter, M. (2005) Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatrica* **94**, 2-15.

132 Sabbagh, M. A. (1999) Communicative intentions and language: evidence from right-hemisphere damage and autism. *Brain Lang* **70**, 29–69.

133 Sandler, R. H., Finegold, S.M., Bolte, E.R., Buchanan, C.P., Maxwell, A. P., Väisänen, M. L., Nelson, M. N., and Wexler, H. M. (2000) Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol*. **15(7)**, 429-435.

134 Savitz, J. Solms, M. Ramesar, R. (2006) The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behavior* **5,** 311-328.

135 Schlemmer Jr., R.F., Narasimhachari, N., and Davis, J.M..(1980) Dose dependent behavioural changes induced by apomorphine in selected members of a primate social colony. *J. Pharmacy Pharmacol.* **32,** 285–289.

136 Shah, A. and Frith U. (1993) Why do autistic individuals show superior performance on the block design task? *J. Child Psychol. Psychiatry* **34(8)**,1351-1364

137 Schneider, M., Retz, W. Freitag, C. Irsch, J. Graf, P. Retz-Junginger, P. Rösier, M. (2007). Impaired cortical inhibition in adult ADHD patients: a study with transcranial magnetic stimulation In: M. Gerlach, Jürgen Deckert, K. Double and E. Koutsilieri (Eds.) Impaired cortical inhibition in adult ADHD patients: a study with transcranial magnetic stimulation* Neuropsychiatric Disorders An Integrative Approach *J. Neural Trans. Suppl.* **72,** 203-309.

138 Shin, L. M., Dougherty, D. D., Orr, S. P., Pitman, R. K., Lasko, M., Macklin, M, L., Alpert, N. M., Fischman, A. J,, and Rauch, S. L. (2000) Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biol. Psychiatry* **48(1)**, 43-50.

139 Shore, S. (2003) *Beyond the Wall*. Autism Shawnee Mission, KS, Asperger Publishing Co.

140 Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., and Frith, C. D. (2004) Empathy for pain involves the affective but not sensory components of pain. *Science* **303(5661)**, 1157-62.

141 Spence, S. A., Hunter, M. D., Farrow, T. F., Green, R. D., Leung, D. H., Hughes, C. J., and Ganesan, V. (2004) A cognitive neurobiological account of deception: evidence from functional neuroimaging. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **359(1451)**,1755-1762.

142 Srinivasan, R., Winter, W. R. Ding, J., and Nunez, P.L. (2007) EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. *J. Neurosci. Methods*. **166**, 41-52.

143 Stone, V. E., and Gerrans P. What's domain-specific about theory of mind? *Social Neurosci.* **1**, 309-319.

144 Takahashi, T. (2008). Biophysics of risk aversion based on neurotransmitter receptor theory. *Neuro Endocrinol. Letters* **29,** 399-404.

145 Tomblin, J. B., Hafeman, L. L., and O'Brien, M. (2003) Autism and autism risk in siblings of children with specific language impairment. *Int. J. Lang. Commun. Disord*. **38(3)** ,235-50.

146 Tononi, G., and Massimini, M. (2008) Why does consciousness fade in early sleep? *Ann. NY Acad. Sci*. **1129**, 330-334.

147 Torrente, F,, Ashwood, P., Day, R. Machado, N., Furlano, R. I,, Anthony, A., Davies, S. E., Wakefield, A. J., Thomson M. A., Walker-Smith, J A,, and Murch, S. H. (2002) Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Molecular Psychiatry* **7**, 375-382.

148 Tucker, D. M., and Williamson, P. A. (1984) Asymmetric neural control systems in human self-regulation. *Psychol. Rev.* **91,** 185–215.

149 Ungerleider, L.G., & Mishkin, M. (1982) Two cortical visual systems. In: D. J.   Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior.* (pp. 549-586). MIT Press, Cambridge, MA.

150 Viggiano, D. Vallone, D., Ruocco, L.A., and Sadile, A. G. (2003) Behavioural, pharmacological, morpho-functional molecular studies reveal a hyperfunctioning mesocortical dopamine system in an animal model of attention deficit and hyperactivity disorder. *Neurosci. Biobehav. Rev.* **27,** 683–689.

151 Vitkovic, L., Konsman, J. P., Bockaert, J., Dantzer, R. Homburger, V. and Jacque, C. (2000) 3Cytokine signals propagate through the brain *Molec. Psychiatry* **5**, 604–615.

152 Volkmar, F.R. (2001) Pharmacological interventions in autism: theoretical and practical issues. *J. Clin. Child Psychol*. **30**, 80–87.

153 Wakefield**,** A. J. Murch**,** S. H. Anthony**,** A. Linnell**,** J. Casson**,** D. M. Malik**,** M., Berelowitz**,** M., Dhillon**,** A. P., Thomson**,** M. A. Harvey**,** P., Valentine**,**   A. Davies**,** S. E. and Walker-Smith**,** J. A. (1997) Ileal lymphoid nodular hyperplasia, non-specific colitis and regressive behavioural disorder: a new syndrome? *J. Pediat. Gastroenterol. Nutrition:* **25(Suppl.)** ,47

154 Watson, K. K., Jones, T. K., and Allman, J. M. (2006) Dendritic architecture of the von economo neurons *Neuroscience* **141**, 1107–1112.

155 Weintraub, S., and Mesulam, M. M. (1983). Developmental learning disabilities of the right hemisphere. emotional, interpersonal, and cognitive components. *Arch. Neurol.* **40,** 463–468.

156 Weir K., and Salisbury, D.M. (1980) Acute onset of autistic features following brain damage in a ten-year-old. *J. Autism Dev. Disord*. **10(2)**, 185-191.

157 Wing, L., and Potter, D. (2002) The epidemiology of autistic spectrum disorders: is the prevalence rising? *Ment. Retard. Dev. Disabil. Res. Rev*. **8(3)**, 151-161.

158 Wong, D.F., Brasić, J.R., Singer, H.S., Schretlen, D.J., Kuwabara, H., Zhou, Y. Nandi, A., Maris, M.A., Alexander, M.., Ye, W., Rousset, O., Kumar, A., Szabo, Z., Gjedde, A., Grace, A.A. (2008). Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacol.* **33,** 1239-1251.

159 Zafeiriou, D. I., Ververi, A., and Vargiami, E. (2007) Childhood autism and associated comorbidities. Brain Dev**. 29(5),** 257-272.

160 Zilbovicius, M., Boddaert, N., Belin, P., Poline, J. B., Remy, P., Mangin, J. F., Thivard, L., Barthélémy, C., and Samson, Y. (2000) Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography. *Am. J. Psychiatry* **157**, 1988-1993.
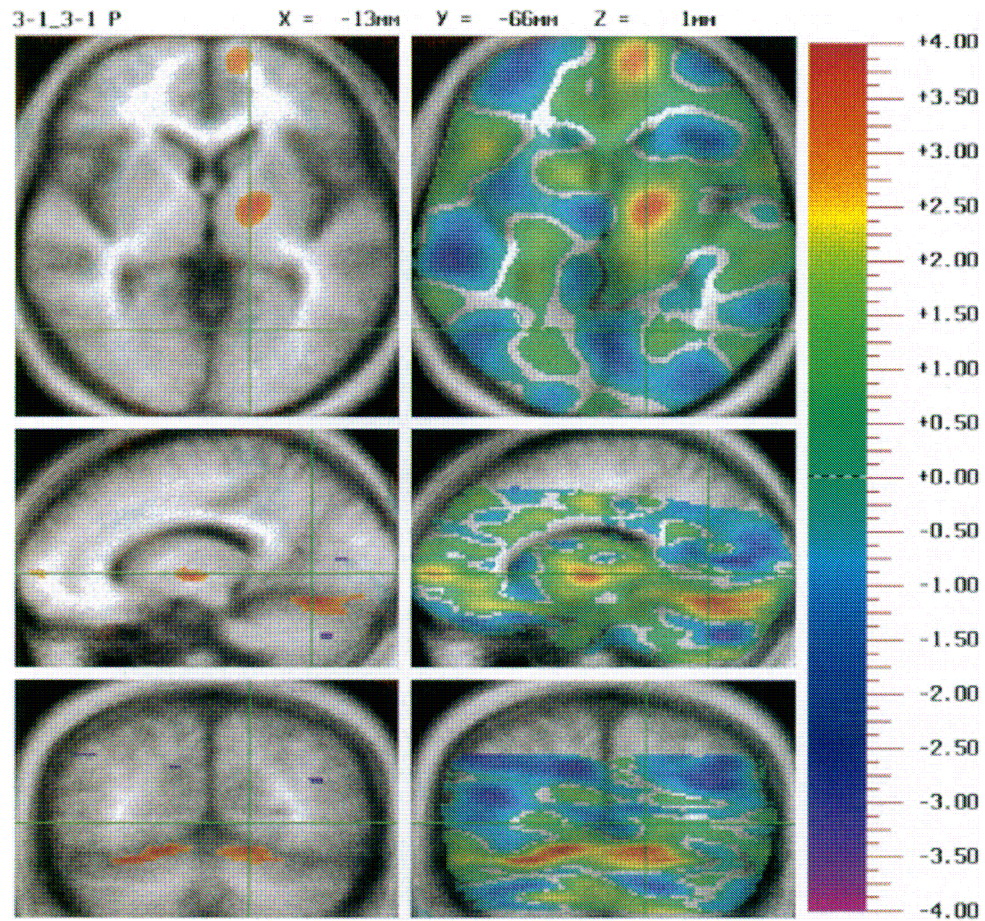
Legend

Figure 1:

The results of the randomisation analysis /4/ used to identify the specific regions where the schizophrenic patients differed from the normal volunteers. Regions in red/yellow tones indicate lower flow in patients during the practiced recall task, while regions in blue indicate higher flow in patients. Results are portrayed using the value of the associated t statistic, shown on the color 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 conceptualised 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 optimisation in the interconnections between nodes. Andreasen and colleagues have indicated that the brains of schizophrenics do not form homogenous connections and networks efficiently resulting in functional disconnectivities. /With permission/

Figure 2:

Right hemisphere model of Autism, ADHD, and Asperger's

Delayed Brain Development
Prenatal maternal stress
Birth trauma
Altered motor development
Sedentary   lifestyle(voluntary/involuntary)
Illness/injury
zenobiotic/toxic exposure
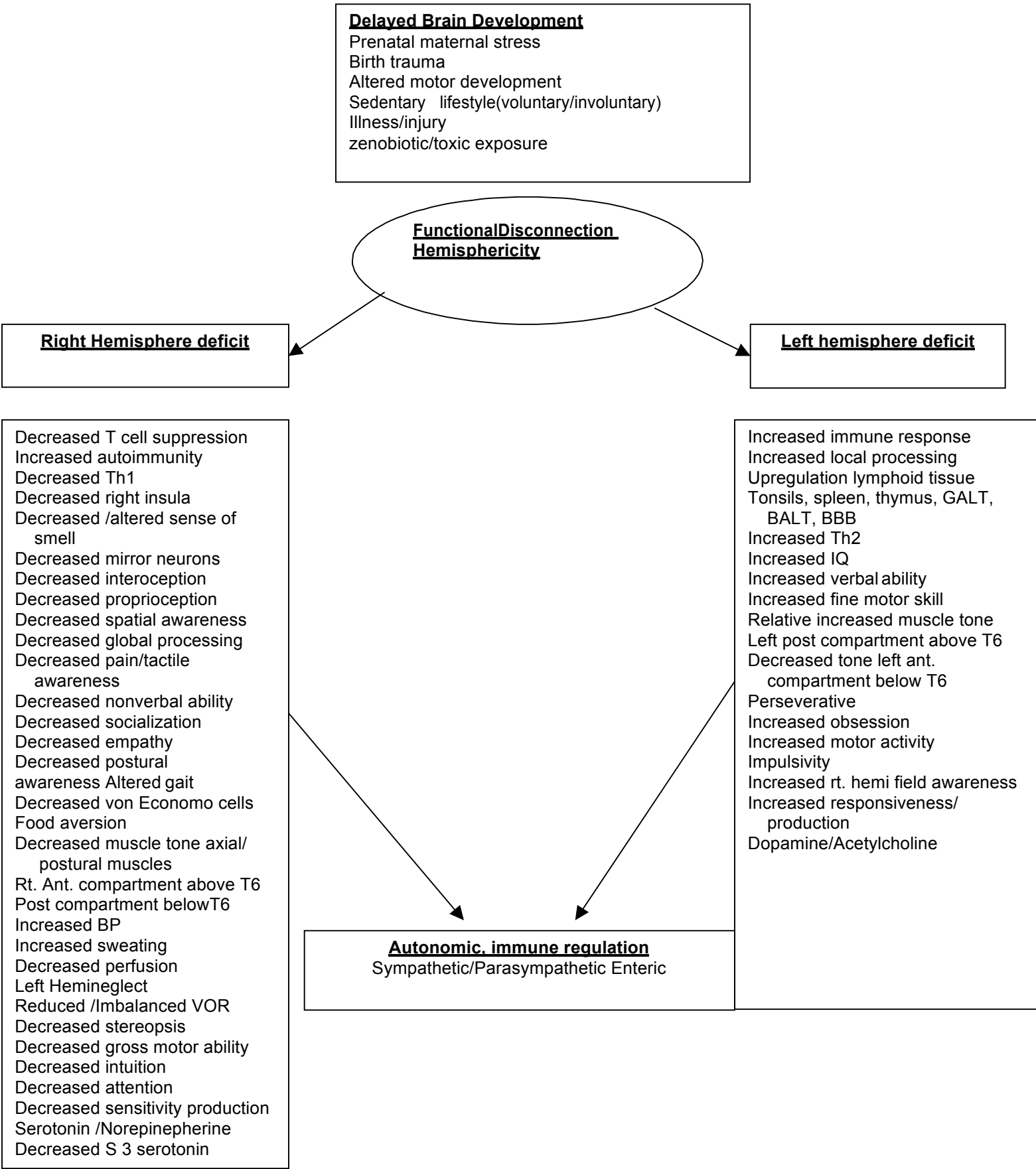
FunctionalDisconnection Hemisphericity

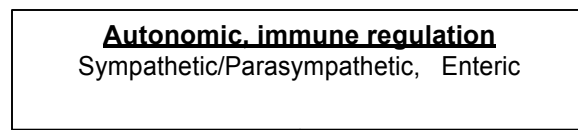**Right Hemisphere deficit**

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. hemi field awareness
Increased responsiveness/
   production
Dopamine/Acetylcholine

Autonomic, immune regulation
Sympathetic/Parasympathetic Enteric

```
          ↘        ↙
┌─────────────────────────────────┐
│   **Autonomic, immune regulation** │
│  Sympathetic/Parasympathetic,  Enteric │
└─────────────────────────────────┘
              │
              ▼
```

Increased sympathetic tone (fight or flight)
Decreased inhibition PVN cells of Hypothalamus
Decreased inhibition IML
Decreased Parasympathetic tone (rest and digest)
Decreased activation of NTS
Decreased secretions (digestive enzymes, HCL, Bile
Decreased peristalsis
Decreased gut motility
Decreased circulation to gut and intestinal lining
Intestinal hyper permeability/gut fragility (leaky gut)
Decreased absorption
Decreased secretory Iga
Decreased barrier functions
Increased polypeptide diffusion
Increased large molecule absorption
Increased activation of Beta adrenergic receptors on
Lymphocytes
Decreased Th1, increased Th2
Decreased NK cell response
Decreased detoxification
Altered Ph
Decreased normal flora
Increased bad bacteria
Increased yeast /fungal growth
Upregulation GALT
Decreased /undigested proteins
Decreased amino acid
Increased opiate polypeptides
Multiple food sensitivities
Increased glucocorticoid
Increased catecholamines
Increased gluconeogenesis
Increased triglyceride
Increased estrodiol in males
Decreased testosterone
Decreased estrogen in females
Increased HPA axis
Increased insulin surges
Decreased insulin sensitivity
Increased heart rate,
Decreased tone of sphincters
Reflux
Decreased vitamin /mineral absorption
Decreased B12, Folate
Anemia
Decreased methylation
Decreased sulfation
Decreased S 3 serotonin receptor

BIOSKETCHES

Robert Melillo is an internationally known lecturer, author, researcher and clinician in the areas of neurology, rehabilitation, Neuropsychology, and neurobehavioral disorders in children. He is also an expert in clinical nutrition with over 20 years of clinical experience. For the past four years, Dr. Melillo has been an adjunct professor of functional neuroanatomy in the graduate doctoral program in Neuropsychology at Touro College and Leeds Metropolitan University. He is also an associate professor of Clinical Neurology and childhood behavioral disorders with The Carrick Institute. He has a master's degree in Neuroscience and is currently completing his PhD in Rehabilitation Neuropsychology. In 2004 Dr. Melillo published his first textbook*, Neuro-behavioral Disorders of Childhood: An Evolutionary Perspective and has authored and* co-authored scientific papers and chapters in texts, pertaining to brain organization in dyslexia, attention, neglect, and learning disorders. He has recently released a book directed at parents and teachers entitled *Disconnected Kids ;The Groundbreaking Brain Balance Program, For Children With Autism, ADHD, Dyslexia And Other Neurological Disorders* from Peragee Publishing. He is currently the executive director of the F. R. Carrick Research Institute, a university based research laboratory that focuses on translational research and development in the areas of neuroscience, brain development, ergonomics and rehabilitation.

Gerry Leisman is Professor of Rehabilitation Sciences at Leeds Metropolitan University in the UK, Scientific Director of the F. R. Carrick Institute for Clinical Ergonomics, Rehabilitation, and Applied Neuroscience and Professor at the University of Haifa in Israel. He was elected Fellow of the American Psychological Society in 1990 and Life Fellow of the American College of Forensic Examination-International in 1994. He has been active since the early 1970s in the promotion of consciousness as a scientifically tractable problem, and has been particularly influential in arguing that consciousness can now be approached using the modern tools of neurobiology and understood by mechanisms of theoretical physics. His primary collaborator in this endeavor has been Paul Koch. He has also been influential in examining mechanisms of self-organizing

systems in the brain and nervous system for cognitive function exemplified by his work in memory, and nervous system optimization. He has likewise applied optimization strategies to movement and gait, cognition, and coma recovery. He is the co-author of a text with Dr. Robert Melillo on Neurobiology and Autistic Spectrum Disorders, has published hundreds of papers in the Cognitive Neuro-, Rehabilitation, Engineering and Systems Sciences and is the holder of patents.

E-mail: g.leisman@alumni.manchester.ac.uk