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PRIMITIVE REFLEXES AND THEIR RELATIONSHIP TO DELAYED CORTICAL MATURATION, UNDER CONNECTIVITY AND FUNCTIONAL DISCONNECTION IN CHILDHOOD NEUROBEHAVIORAL DISORDERS

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ABSTRACT

Persistent primitive reflexes have been noted in a number of neurobehavioral disorders and are thought to be related to delayed or absent developmental milestones in this population of children. This is also associated with the presence of clumsiness, incoordination, awkward posture, gait and other motor disturbances. The degree of motor incoordination seems to be related to cognitive dysfunction as well. ADHD, autism, dyslexia as well as almost all neurodevelopmental disorders have been associated with anatomical and functional effects that correlate with the motor incoordination, motor disturbance, cognitive delays and the presence of persistent primitive reflexes. For some time researchers have debated if the structural anatomic and volumetric differences in disorders such as ADHD and autism represent deviant developmental changes or whether they reflect a maturational delay. In this paper we review the literature that clearly demonstrates that these disorders and the structural differences represent cortical maturational delays not deviant development. We also note that persistent primitive reflexes are the earliest markers for this delay and that this delayed maturation will eventually lead to the presence of autism, ADHD, and other neurobehavioral disorders. We also note that these disorders and their recent reported increased incidence is related to a combination of genetic and epigenetic factors mostly driven by environmental and lifestyle changes affecting early motor development, sensory stimulation and activity dependent synaptogenesis and neuroplasticity. Symptom variations between these neurobehavioral disorders may be related to asymmetrical maturational differences resulting from different rates of maturation of the right and left hemisphere. Asymmetric persistent primitive reflexes may also be an early marker related to this maturational imbalance.

This abnormal pattern of hemispheric asymmetry may lead to desynchronization, underconnectivity, and

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ultimately a functional disconnection between regions of the brain and cortex. Lastly we comment of the possibility of exercises that can inhibit and remediate persistent primitive reflexes as one possible target for early treatment of these disorders.

Keywords: ADHD, Autism, functional disconnection, primitive reflexes, maturational lag.

INTRODUCTION

ADHD is thought to be the most prevalent childhood disorder. In 2010 the National Institute of Mental Health stated that ADHD is the most prevalent mental disorder among the youth in the US [1]. The US Center for Disease Control recently stated that ADHD now affects 10 % of all children in the United States [2]. Although some of the increased prevalence may be related to changes in diagnostic criteria and increase awareness that is not sufficient to explain the geometrically increased incidence. Autism two decades ago was diagnosed in 1-10,000 children, most recent statistics from the CDC now stated the prevalence as 1-110 or 1% of the population [2]. Although some genetic differences have been identified between ADHD and non-ADHD children, these differences are only present in a relatively small percentage, the relationship to ADHD symptoms has not been demonstrated, and their mechanisms of action is speculative at best [3]. For the vast majority of cases of ADHD and autism there is no clear genetic cause. Although ADHD and autism both seem to have a relative high concordance within families, many researchers think that environmental epigenetic influences are the primary driving forces behind the rapid increase in ADHD and other neurobehavioral disorders such as autism, Tourette's and others [3].

Recent research has attempted to clarify whether specific differences in the size and function of the brains of those with ADHD and autism are related to deviant developmental changes or whether they reflect a maturational delay [4]. In this paper we review the literature in regard to this question and identify other markers of development, specifically persistent primitive reflexes and delayed or absent motor milestones, that might reflect maturational delay. We will also identify particular targets of therapeutic intervention based on these markers. We will also discuss this maturational delay and its relationship to the concept of functional disconnection, which we hypothesize to be the neurophysiologic mechanism associated the symptoms of ADHD.

Human executive functions are unique among all organisms. Humans have achieved a level of "intelligence" which reflected in self-consciousness or self-awareness beyond the degree achieved by other species. These unique cognitive abilities do not appear to be a product of genetic differences since we share 85% of the same genes as mice and 99% of the same genes as chimpanzees yet our cognitive abilities or intelligence is arguably exponentially different than that of a chimpanzee. Many neurobehavioral disorders of childhood are thought to be partly the result of the delayed maturation or development of executive functions. Tannock and Schachar [5] note, "that there is a growing consensus that the fundamental problems in (ADHD) are in self-regulation and that ADHD is better conceptualized as an impairment of higher-order cognitive processing known as (executive function).

What is clear in the literature is that the main functions that are affected have been termed executive functions and it is known that executive functions seem to primarily reside in the frontal lobes. In fact, ADD is

considered a name for a spectrum of deficits of cognitive executive functions that may respond to similar treatments and are often comorbid with a wide variety of psychiatric disorders, many of which may also be spectrum disorders.

Therefore understanding how executive functions arose through the course of evolution may provide insight as to why delays in development may occur during the course of childhood. Ontogeny recapitulates phylogeny, also known as "Biogenetic Law" was proposed by Ernst Haeckel in 1866. Although this theory has been discredited there are many similarities between development of the human brain during childhood and its development during the course of evolution. To explore this concept further we must explore the question, when and brains develop the way that they did through the course of evolution which can then provide insight into the development of the human brain and its executive functions.

According to Llinaes [6,7], brains and a nervous system are only necessary for multicellular creatures that can orchestrate and express active movement, a biological property known as (motricity). For movement to be beneficial it must be purposeful or goal directed otherwise it will not be beneficial and will not be selected out by natural selection. Once one moves, one must make a choice to move either toward or away requiring a choice which requires some level of prediction. For movement to purposeful and beneficial it must be able to predict the outcome of movement before it occurs. This requires what we refer to as thinking. Prediction or goal directed behavior is thought to be the foundation of all executive function. Approach or avoidance is the foundation of all behavior and has been present from the very beginning; this is the beginning of asymmetry in the brain. There is a simple rule in evolution: simple movement simple brains, complex movement complex brains.

Movement allows us to interact with the environment in more sophisticated ways and can help improve our chances of survivability. Interacting with the environment in a purposeful and beneficial way requires the development of sensory organs which supply us with information about our environment allowing us to negotiate our environment and develop a sensory motor map of the world that we can use as the basis of prediction and goal directed adaptive behavior.

As we interact with our environment developmentally in progressively more sophisticated ways, we develop our sensory systems through feedback with the outside world. This in turn will activate genes that will cause activity-dependent neuronal plasticity increasing the size, complexity and integration of the brain to allow for a more accurate picture of the environment and more accurate predictions of the outcome of movement allowing for greater survivability. The nature of the relation of enrichment on plasticity has been more fully described in another paper by Leisman [8] in this issue.

Organisms developed brains because they moved and as they moved they interacted with their environment. Human beings, as a species, have a large brain that is capable of a high cognitive intelligence, and an upright body position that is propelled by bipedalism. Walking upright allows for less leeway in size and structure in the human pelvis than exists for those animals that walk on all fours. Large headed infants are born to mothers with relatively constrained birth canals. If both mother and neonate are to survive the birth process unscathed, the infant's brain cannot be fully developed in size or complexity at birth. No matter how precocious we may fancy that our children are, no human infant is as precocious as a horse's newborn foal or a

duckling recently hatched, that can run or swim when only hours old, humans are unable to do much more than feed and interact with their caregivers until after several months of life have passed.

Our newborn skull is only a quarter the size that it will become in the adult. It weighs approx. 370 grams at birth and will nearly triple to 1080 grams by age 3, and quadruple to 1350 grams by six to 14 years. "The brain comprises 100 billion neurons at birth, with each neuron developing on average 15,000 synapses by 3 years of age." [9] Much of the growth of the brain; and the concomitant expansion of the head will have occurred by the age of 2 years at which age the cranium is 75% of its adult size and volume, and the brain is about 80% of its adult weight. By approximately 10 years of age, the brain (and skull) reaches approximately 95% their ultimate adult size. Overall, the human brain more than triples in size from birth to adulthood. Therefore, humans are born with considerably less than their ultimately fully developed brains. Our brains are "built" during child and adolescent development.

To stimulate growth and development of the brain an infant needs to be able to move and interact with his environment. However, the process of movement is impeded by a brain and nervous system that is not effectively developed at birth and when little functioning motor cortex exists that can control volitional movement. What makes some volitional movement possible are the infantile "primitive reflexes" already intact at birth that allow for reflexogenic movement and interaction with the environment in basic ways that help increase the chances of survival. These reflexes appear prenatally and are thought to aid in the birth process. Most of these reflexes are present at birth and then become inhibited within the first few months with the longest (the plantar reflex) remaining until the end of the first year post-natally. These reflexes allow for basic reflexogenic movement thought to contribute to early motor milestones such as rolling over, creeping, crawling, grasping, sucking and eventually crawling and walking.

Postural reflexes that allow for more sophisticated individualized movements are themselves replaced with voluntary movement. Primitive reflexes allow for basic movements, which allow for simple interaction with the environment and form the basis of early movement. This movement allows the infant to interact with his environment and engages and stimulates his sensory organs and receptors. This increase in sensory feedback and stimulation is thought to result in the expression of genes that are related to protein synthesis and the building of functional connections and the stimulation of glial cell proliferation and increasing the size and connectivity of neurons. [10] As neurons grow in size, density and connectivity they will eventually inhibit, through propriospinal projections, lower or more primitive areas of the brain and will stimulate the growth and activation of higher more sophisticated areas in higher and higher rostral areas of the brainstem and cortex [11]. Primitive reflexes eventually become inhibited but they are never completely eliminated. Eventually all reflexes seem to come under control of the frontal lobe. [12]

In patients with frontal lobe damage, dysfunction, or degeneration there is often the reappearance of primitive reflexes known as frontal release signs [12]. Upper motor lesions also often result in the reappearance of primitive reflexes such as the Babinski reflex or plantar reflex. This is thought to be due to the loss of the inhibitory descending connections from the cortical spinal tract, which is a reflection of the maturation and growth of the frontal lobe and the sensory motor cortex [13].

Primitive and postural reflex testing is part of a typical pediatric neurological examination and it is commonly known that the persistence of these reflexes is associated with brain damage or injury.

However it has also been noted [14] that the presence of these reflexes is a common feature of children with neurodevelopmental disorders of childhood such as ADHD and autism. In most of these disorders there no observable damage, injury, lesion or degeneration is present resulting in our here hypothesizing that the persistence of these primitive reflexes reflects a maturational delay of areas of the brain that would normally inhibit these reflexes especially those in feedback with the frontal lobes.

The maturational delay of the frontal lobes is reflected by the persistence of primitive reflexes and delay in the development of postural reflexes, which in itself leads to the delay of various motor and sensory milestones like crawling and walking. Maturational delay is also related to the lack of development of executive functions, a hallmark of ADHD and other neurodevelopmental disorders. This maturational lag is thought to be a product of abnormal or absent environmental influences that will alter gene expression resulting in smaller, more immature neurons associated with underconnectivity, decreased activation, coordination and synchronization of cortical networks which we think underlies the symptoms and functional deficits seen in children with ADHD and other neurodevelopmental disorders.

One of the other unique features of the human brain is its degree of lateralization or asymmetry. Humans have the most asymmetrical and lateralized brains of any species [15]. This is thought to be another factor that leads to the significant differences in cognitive intelligence between humans and other species. Having a more lateralized brain allows for the development of a greater variety of centers that can individually process and control various functions, being able to combine these unique individual centers together into various combinations leading to the unique cognitive abilities of humans. This lateralization becomes more developed with increasing age and development of the brain and nervous system.

A small child does not have the same degree of laterality as an adult [16]. Laterality is in many ways a product of maturity of the brain and especially of the neocortex and the frontal lobes [16]. The development of laterality and asymmetric control of functions increases cognitive potential but also requires greater coordination and synchronization of cortical networks [17]. For various functions to bind together there must be activation of all of these areas and their networks simultaneously. This coordination is also a byproduct of maturity. As the brain grows and as neurons become interconnected, the speed and coordination of cortical networks inter- and intra-hemispherically increases, allowing for synchronization and integration of greater numbers of functions. The two hemispheres of the brain do not develop at the same time [18]; the right hemisphere is thought to develop more rapidly and earlier than the left with the greatest development being prenatal and for the first 2-3 years of life. Then the left hemisphere is emphasized in development for the next 2-3 years. Development will continue this back and forth development between the two hemispheres until adolescence.

Environmental influences that appear during different time courses of development are thought to contribute to the growth and development of the brain and the cerebral hemispheres. The type of environmental and sensory stimulation available during a particular phase of

development will influence the receptors that are activated and the cortical networks that will ultimately process that information. The hemisphere that is being emphasized during a particular phase of development will be the hemisphere that will ultimately have an advantage for processing that type of information and will develop as a product of that incoming flow of sensory information.

The absence or reduction of environmental influences that would normally promote the growth and development, and neuroplasticity within higher centers, would normally lead to the inhibition of primitive reflexes and the expression of postural reflexes. The persistence of these primitive reflexes is a reflection of a maturational lag, which, in turn, is a result of not activating gene expression that would ultimately lead to the growth and development of neurons and their connections. Depending on when during development primitive reflexes are "turned off" will influence hemispheric development and specialization as well. The persistence of primitive reflexes especially asymmetric persistence will be a reflection of not only maturational delay of the brain but, depending on the timing, may indicate an abnormal asymmetrical development of the hemispheres.

If this happens in the first two to three years of life, it will be more likely to result in a maturational delay of the right hemisphere. This will result in a physical immaturity of the brain and brain stem that may be measured as a volumetric difference, but, we hypothesize, will also lead to under connectivity and lack of coordination and synchronization with other cortical networks both within the right and left hemisphere and between the two hemispheres. The long range cortical connections, exemplified in Figure 1, form later in development [19] and are thought to contribute to the temporal coherence of cortical networks especially between the two hemispheres. These long range cortical networks forming after the shorter range connections, are found more between the two hemispheres and are expected to be more affected and underdeveloped with maturational delays [16].

This may lead to greater coherence within the hemisphere while there will be less coherence between the hemispheres [16, 20]. This is the foundation of a functional disconnection, which we think is basis of many of the symptoms of neurodevelopmental disorders of childhood. The difference in symptoms is dependent on the hemisphere that is underdeveloped and the timing of the epigenetic influences that affect that development.

PRIMITIVE REFLEXES

Primitive reflexes are considered adaptive reactions that appear in neonatal life and disappear or are inhibited as the brain matures. Their persistence and or reappearance in childhood, adolescence and adulthood is thought to indicate cortico-subcortical neuronal loss or possibly neuronal developmental delay that may be associated with normal aging or dementia. [21-28]. Some authors have stated that these reflexes are found in normal populations. Even in young adults the palomental reflex was found in 6% to 27% of subjects aged 20 to 50 years, and 28% to 60% of those above 60 years; snouting in 13% of subjects between 40 and 57 years and 22% to 33% of those above 60 years of age; [29] and suck reflex which some authors associate with "frontal lobe disease," has been found in 6% or more of normal subjects aged 73 to 93 years. [22] Therefore the prevalence of these reflexes is considered to be variable and

there is disagreement on the pathological significance of these reflexes, and on their increasing frequency with aging.

The grasp reflex and the extensor plantar response (Babinski sign) are two reflexes that are well established as indicators of disease in the central nervous system. It is possible that some of the controversies may be explained by differences in opinion and interpretation of the reflexes which can vary significantly from clinician to clinician [30], leading to variability in what is considered "normal." It may be that an individual with early functional neurological impairments or children with subtle developmental delays may still fall within the "normal" range for the majority of tests yet actually be showing the beginnings of what may later develop into a pathological state. Perhaps then these signs can be viewed as early markers for developmental delay or for neurological dysfunction. The relationship between cognitive deficits and primitive reflexes has also been controversial. Some authors [22, 23] consider these reflexes as predictive of diffuse cerebral dysfunction, since these signs are significantly correlated with cognitive deficits in a wide age-range of individuals as determined by the Halstead-Reitan neuropsychological test battery.

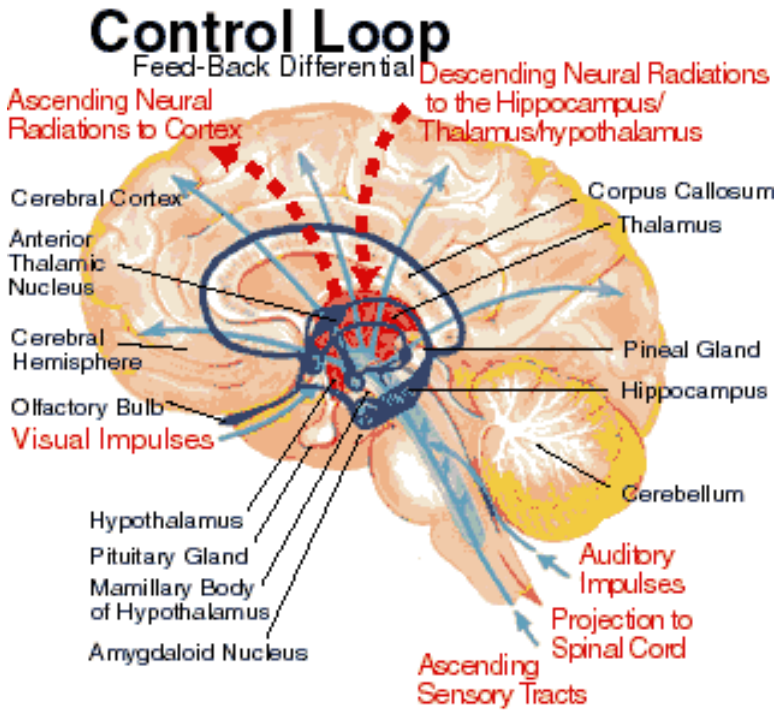

Figure 1. The Reticular Activating System and its connections. The Reticular Activating System appears to be intimately involved in the neural mechanisms which produce consciousness and focused attention, receiving impulses from the spinal cord and relaying them to the Thalamus, and from there to the Cortex, and back again in a feedback loop to the Hippocampus/Thalamus/ Hypothalamus and participating neural structures in order for learning and memory to take place. Without continual excitation of cortical neurons by reticular activation impulses, an individual is unconscious and cannot be aroused. When stimulation is enough for consciousness but not for attentiveness, ADD or LD results. If too activated, an individual cannot relax or concentrate (and is over-stimulated or hyperactive) often resulting in ADHD.

On the other hand, other authors found no correlation between snout, glabellar, and grasp reflexes and the presence of cerebral atrophy by CT-scan or by the results of psychometric tests (Wechsler Memory Scale) in patients with Alzheimer's disease. [31] In another study, the relationship between primitive reflexes (PRs) and cognitive functioning was examined in aging individuals with and without dementia, to verify what items of neurological examination and cognitive testing were the most predictive of brain dysfunction. Using the Cognitive Abilities Screening Instrument-Short Form (CASI-S), Teng and colleagues, [32] concluded that in those with dementia, the highest primitive reflex scores tended to associate with the lowest cognitive scores and in particular to SPECT scan pattern. Therefore, these researchers concluded that the presence of multiple PRs and their scores could be useful predictors of diffuse cerebral dysfunction. In particular the presence of the grasp and Babinski responses, or the combination of paratonia, snout, suck, and palomental reflexes are strong indicators of diffuse brain dysfunction, especially when these signs are marked and accompanied by deficits of one or more of the cognitive subsets. If the presence of multiple primitive reflexes is an indicator of diffuse brain dysfunction in elderly populations, it is possible that their persistence and presence in children and adolescence may be indicative of diffuse cortical maturational delay, and correlate with cognitive ,and executive developmental absence or delay?

Primitive Reflexes and Delayed Cognitive and Motor Development

There has been a correlation shown between retained primitive reflexes and delayed motor development in very low birth weight infants. [33] The asymmetrical tonic neck reflex, tonic labyrinth reflex and Moro reflex were assessed in low birth weight children. They observed the children's ability to roll and measured their performance on the gross motor scale of the Denver Developmental Screening Test. Marquis and colleagues [33] noted that very low birth weight (VLBW) infants retained stronger primitive reflexes and exhibited a significantly higher incidence of motor delays than did full-term infants. They confirmed a high incidence of motor delays among VLBW infants and demonstrated a clear association between retained reflexes and delayed motor development in VLBW infants. It is important to note that this was in the absence of any overt pathology in the brains of these children.

In another study [34] the relationship between extreme low birth weight infants, motor and cognitive development at one and at 4 years was studied. The authors note that a relationship between motor ability and cognitive performance. Their study investigated the association between movement and cognitive performance at one and 4 years corrected age of children born less than 1000g, and whether developmental testing of movement at one year was predictive of cognitive performance at four years. Motor assessment at both ages was performed using the neurosensory motor developmental assessment (NSMDA). Cognitive performance was assessed on the Griffith Mental Developmental Scale at one year and McCarthy Scales of Children's Abilities at four years. A significant association was found between NSMDA group classification at one year and cognitive performance at both one and at four years and between the subscales of each test. They also noted that group classification of motor development at one year was predictive of cognitive performance at four years and this was

independent of biological and social factors and the presence of cerebral palsy.

In yet another study, [35] the relationship between a normal intact cerebellum and primitive reflexes was examined. Tonic labyrinth and neck reflexes were studied separately and in combination in the decerebrate cat before and after acute cerebellectomy. The investigators noted clear changes in these reflexes both before and after surgery. They concluded that the presence of the cerebellum is required for the occurrence of the normal asymmetric labyrinth reflexes. As we will show later, decreased size and immaturity as well as dysfunction of the cerebellum and the inferior olive are seen in almost all children with neurobehavioral disorders and these factors are thought to play a critical role in the development of normal coordination and synchronization of the motor system and the brain.

Romeo and associates [36] examined the relationship between the acquisition of a postural reflex, the forward parachute reaction (FPR), and the age of acquisition of independent walking. They noted that most of the infants they examined had a two step development pattern. The infants at first showed an incomplete and then a complete FPR which was observed more frequently at nine months. An incomplete FRP only, without successive maturation to a complete FPR was present in 21% of the whole sample. Infants with a complete FPR walked at a median age of 13 months, whereas those with an incomplete FPR only walked at a median age of 14 months. The investigators observed, in those with incomplete pattern, a trend toward delayed acquisition of independent walking.

Teitelbaum and associates, [37] hypothesized that movement disturbances in infants can be interpreted as "reflexes gone astray" and may be early indicators of autism. They noted that in the children they reviewed, some had reflexes that persisted too long in infancy, whereas others first appeared much later than they should. The asymmetric tonic neck reflex is one reflex that they noted may persist too long in autism. Head verticalization in response to body tilt they noted is a reflex that does not appear when it should in a subgroup of "autistic-to-be" infants They suggested that these reflexes may be used by pediatricians to screen for neurological dysfunction that may be a markers for autism.

In their earlier work earlier work, [38] they showed that infants destined to become autistic showed a characteristic cluster of disturbances in movement patterns detectible by our methods as early as 4-6 months of age. Teitlebaum et al. Eshkol-Wachman Movement Analysis (EWMN) [39], in conjunction with laser disc still-frame analysis. They suggested that the movement disturbances noted in autism can be understood as reflexes gone astray in infancy.

Relationship between Motor Incoordination and ADHD/Autism

We have elsewhere described how abnormal motor development can accurately be used as a marker to predict autism in later development [8]. Many authors have noted a relationship between incoordination and clumsiness, especially of posture and gait, and autism as well as with other neurodevelopmental disorders. The type of gait and motor disturbance has been compared mostly to those that are either basal ganglionic and most commonly cerebellar in origin. [40] The most common of all comorbidities in practically all neurobehavioral disorders of childhood is *DCD*, developmental coordination disorder, or more simply put "clumsiness" or motor incoordination. In fact, practically all

children in this spectrum have some degree of motor incoordination. The type of incoordination is also usually of the same type primarily involving the muscles that control gait and posture or gross motor activity. Sometimes to a lesser degree, we find fine motor coordination also affected.

Although it has been fairly well known that attention deficit disorders are comorbid with psychiatric disorders such as the ones described above, what is less known and what is more significant is the association between *ADD* and motor controlled dysfunction (clumsiness) or developmental coordination disorder. [41] In the past, motor clumsiness had not been viewed as a psychiatric disorder, but rather being neurological. Motor control problems were first noted in what were then called minimal brain dysfunction syndromes or MBD. MBD was the term used to describe children of normal intelligence, but with comorbidity of attention deficit and motor dysfunction or "soft" neurological signs. Several studies by Denckla and others [42-48] have shown that comorbidity exists between *ADHD* and *OCD*, dyscoordination and/or motor perceptual dysfunction. Several studies have shown that 50 percent of children with ADHD also had OCD .[49]

In a Dutch study, [50] 15 percent of school age children were judged to have mild neural developmental deviations and another 6 percent demonstrated severe neural developmental deviations (occurring in boys twice as often as in girls). Minor developmental deviations were reported to consist of dyscoordination, fine motor deviations, choreiform movements, and abnormalities of muscle tone. Researches that have dealt with these minor neural developmental deviations tend to look at motor dysfunction as a sign of neurological disorder that may be associated with other problems such as language and perception dysfunction. Motor dyscoordination has also been noted as a significant sign in autistic spectrum disorders and in Asperger's syndrome. In fact, it has been speculated that the type of motor incoordination might be able to differentiate high functioning autistic from Asperger's syndrome individuals. [51-53]

In Asperger's syndrome, it has been noted that individual's have significant degrees of motor incoordination. In fact, in Wing's original paper, she noted that of the 34 cases that she had diagnosed based on Asperger's description, "90 percent were poor at games involving motor skill, and sometimes the executive problems affect their ability to write or draw." Although, gross motor skills are most frequently affected, fine motor and specifically graphomotor skills were sometimes considered significant in Asperger's syndrome." [54, 55] Wing [55] noted that posture, gait, and gesture incoordination was most often seen in Asperger's syndrome and that children with classic autism seem not to have the same degree of balancing and gross motor skill deficits. However, it was also noted that the agility and gross motor skills in children with autism seem to decrease as they get older and may eventually present in similar or at the same level as Asperger's syndrome.

Gillberg [56] also reported clumsiness to be almost universal among children that she had examined for Asperger's syndrome. The other associated symptoms she noted consisted of severe impairment and social interaction difficulties, preoccupation with a topic, reliance on routines, pedantic language, comprehension, and dysfunction of nonverbal communication. In subsequent work, Gillberg included clumsiness as an essential diagnostic feature of Asperger's syndrome. [57-59]

It has been reported [59] that children with ADHD and autism spectrum problems, particularly those given a diagnosis of

Asperger syndrome, have a very high rate of comorbid Developmental Coordination Disorders. Klime and colleagues [60] noted that a significantly higher percentage of Asperger's rather than non-Asperger's autistic individuals showed deficits in both fine and gross motor skills either relative to norms or by clinical judgment. They further noted that all 21 Asperger's cases showed gross motor skill deficits, but 19 of these also had impairment in manual dexterity which seems to suggest that poor coordination was a general characteristic of Asperger's. With studies like these, many researches have noted dysfunction of fine motor coordinative skills as a feature of autistic spectrum disorders.

However, when we examine the condition from the perspective of the interaction of the cerebral hemispheres, as we will note later, gross motor skill dysfunctions are more typical of right hemisphere involvement whereas fine motor skill dysfunctions are more typical of left hemisphere involvement.

We will demonstrate later that both classic autism and Asperger's syndrome are associated with right hemisphere deficits, and thereby, would be expected to show a greater involvement of gross motor skill deficits.

It might seem somewhat confusing initially when fine motor skills seem to be disrupted at almost equal levels. According to a neuropsychological model, this type of weakness would be more indicative of a left hemisphere deficit. However, when examining the literature closely, it has been noted [61] that manual dexterity is less effective for high functioning autistics than for Asperger's, but only for the non-dominant hand. This suggests a lateralized difference. This would show that although fine motor coordinative skill is decreased in autistics, it is primarily decreased in the left hand, associated with right hemisphere function. This is consistent with a hemispheric imbalance model and specifically a right hemisphericity.

Manjiviona and Prior [62] noted that 50 percent of autistics and 67 percent of their Asperger's individuals studied presented with significant motor impairment as defined by norms on a test of motor impairment. Szatmari and colleagues [61, 63] also noted that autistic groups did not differ from Asperger's groups with respect to dominant hand speeds on type boards although both were slower than psychiatric controls. Vilensky and associates [64] analyzed the gait pattern of a group of children with autism. They used film records and identified gait abnormalities in these children that were not observed in a controlled group of normally developing children or in small groups of "hyperactive/aggressive children."

Reported abnormalities were noted to be similar to those associated with Parkinson's. Hallet and colleagues [65] assessed the gait of five high functioning adults with autism compared with age matched normal controls. Using a computer assisted video kinematic technique; they found that gait was atypical in these individuals. The authors noted that the overall clinical findings were consistent with a cerebellar rather than a basal ganglionic dysfunction.

Kohen-Raz and colleagues [66] noted that postural control of children with autism differs from that of matched mentally handicapped and normally developing children and from adults with vestibular pathology.

These objective measures were obtained using a computerized posturographic technique. It has been also noted that the pattern of atypical postures in children with autism is more consistent with a mesocortical or cerebellar rather than vestibular pathology.

Numerous investigators [67] have provided independent empirical evidence that basic disturbances of the motor systems of individuals with autism are especially involved in postural and lower limb motor control.

Makris et al, [68] examined attention and executive systems abnormalities in adults with childhood ADHD. They noted that ADHD is hypothesized to be due, in part, to structural defects in brain networks influencing cognitive, affective, and motor behaviors. Although the literature on fiber tracts is limited in ADHD, they note that gray matter abnormalities suggest that white matter connections may be altered selectively in neural systems.

A prior study, [69] using diffusor tensor magnetic resonance imaging showed alterations within the frontal and cerebellar white matter in children and adolescents with ADHD.

In this study of adults the authors hypothesize that fiber pathways subserving attention and executive functions would be altered. To this end, the cingulum bundle (CB) and superior longitudinal fascicle II (SLF II) were investigated in vivo in 12 adults with childhood ADHD and 17 demographically comparable unaffected controls using DT-MRI.

Relative to controls, the fractional anisotropy (FA) values were significantly smaller in both regions of interest in the right hemisphere, in contrast to a control region (the fornix), indicating an alteration of anatomical connections within the attention and EF cerebral systems in adults with childhood ADHD.

The demonstration of FA abnormalities in the CB and SLF II in adults with childhood ADHD provides further support for persistent structural abnormalities into adulthood.

ADHD, Executive Function and Cortical Maturation

McAlonan et al. [70] noted that children with attention-deficit hyperactive disorder (ADHD) have difficulties with executive function and impulse control which they postulate may improve with age which would seem to correlate to a maturational delay rather than structural damage. In this study they compared ADHD and control groups on the change task measures of response inhibition (stop signal reaction time SSRT) and shifting (change response reaction time, CRRT). Voxel-wise magnetic resonance imaging correlations of reaction times and grey matter volume were determined, along with bivariate correlations of reaction times, brain volumes and age. Results showed that individuals in the ADHD group had longer SSRTs and CRRTs.

Anterior cingulate, striatal and medial temporal volumes highly correlated with SSRT. Striatal and cerebellar volumes strongly correlated with CCRT. Older children had faster reaction times and larger regional brain volumes. In controls, orbitofrontal, medial temporal and cerebellar volumes correlated with CCRT but not SSRT. The authors concluded that this evidence supports delayed brain maturation in ADHD and implies that some features of ADHD may improve with age.

Shaw et al [71] noted that there is a controversy over the nature of the disturbance in brain development that underlies ADHD. They note that it is unclear to some whether the disorder results from a delay in brain maturation or whether the disorder results from a deviation from the template of typical development. Since its earliest description, there has been debate as to whether the disorder is a consequence partly of delay in brain maturation or

complete deviation from typical development. [72] Several studies find that brain activity at rest and in response to cognitive probes is similar between children with ADHD and their slightly younger but typically developing peers, evidence that would seem to be consistent with a maturational lag in cortical development. [73-74] Others report a quantitatively distinct neurophysiology, with a unique architecture of the electroencephalogram and some highly anomalous findings in functional imaging studies which would seem to imply that ADHD is a deviation from typical development. [75-79] Using computational neuroanatomic techniques, Shaw and colleagues [71] they estimated cortical thickness at >40,000 cerebral points from 824 magnetic resonance scans acquired prospectively on 223 children with ADHD and 223 typically developing controls. With this sample size, they could define the growth trajectory of each cortical point, delineating a phase of childhood increase followed by adolescent decrease in cortical thickness (a quadratic growth model).

The findings are exemplified in Figure 2. From these trajectories, the age of attaining peak cortical thickness was derived and used as an index of cortical maturation. They found maturation to progress in a similar manner regionally in both children with and without ADHD, with primary sensory areas attaining peak cortical thickness before polymodal, high-order association areas. However, there was a marked delay in ADHD individuals in attaining peak thickness throughout most of the cerebrum: the median age by which 50% of the cortical points attained peak thickness for this group was 10.5 years, which was significantly later than the median age of 7.5 years for typically developing controls. The delay was most prominent in prefrontal regions important for control of cognitive processes including attention and motor planning. Neuroanatomic documentation of a delay in regional cortical maturation in ADHD has not been previously reported.

Immaturity in functional connectivity measures had previously been reported in studies of other developmental disorders including autism. [80-85] At present it remains unclear whether these immaturaties are common across different developmental disorders or whether or not they involve the same or similar brain regions. It may be that functional connectivity studies are documenting immaturities in different functional networks or different parts of the same networks. [86] ADHD is commonly comorbid with Tourette's syndrome and it is possible the two disorders share a common connectivity deficit that becomes apparent in both in studies that examine at both ADHD and Tourette's). [87,88]

It has been suggested more generally that long–range functional underconnectivity could be related to deficits in the integration of information [87,88]. The decrease in long range connections observed in Tourette's adolescents relative to their age–matched peers is consistent with this idea as well. [86]. In this scenario functional underconnectivity could affect communication and coordination between the cerebellum, frontal cortex, and parietal cortex. Different patterns of functional connectivity might explain distinctive symptoms in different developmental disorders. Some authors [86] have noted that the connectional immaturity observed in TS is not due to a general functional underconnectivity, but rather to a more specific pattern of increasing and diminishing functional connections that appear to mimic the pattern observed in studies of typical development [88].

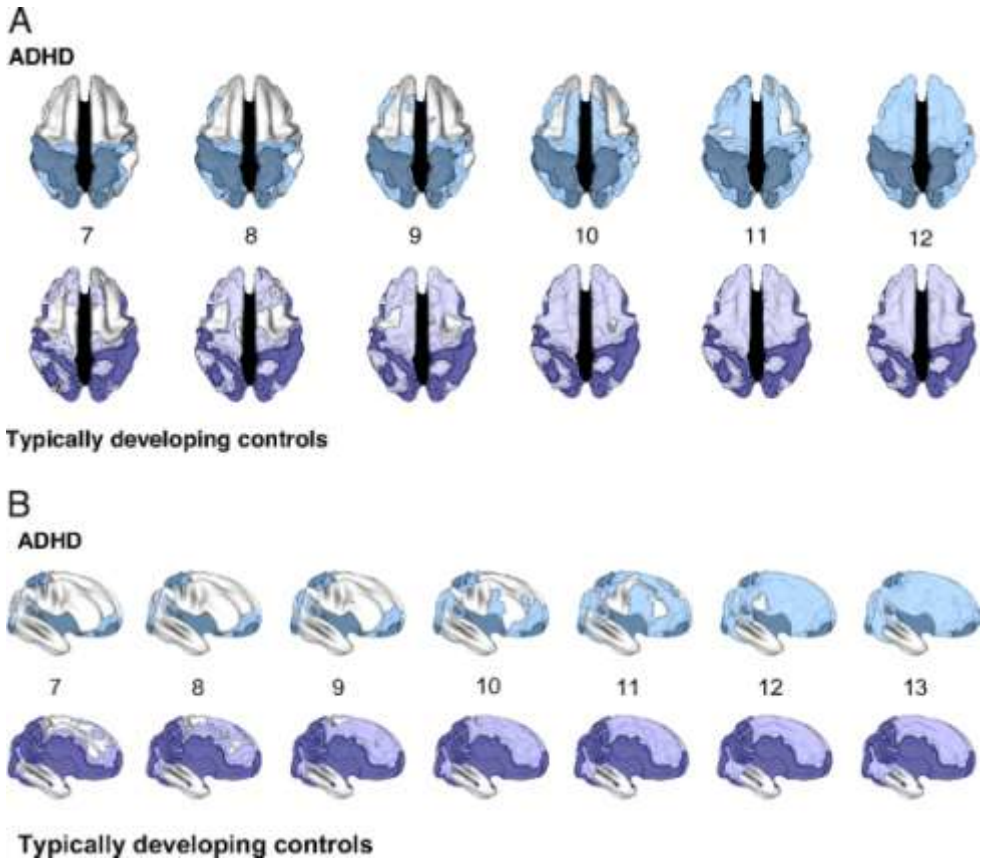

Figure 2. The age of peak cortical thickness in children with ADHD compared with normals. *(A*) dorsal view of cortical regions of peak thickness by age (ages 7–12) in ADHD (*Upper*) and normal controls (*Lower*). Darker colors indicate regions where a quadratic model was not appropriate (non-calculated peak), or the peak age was estimated to lie outside the age range covered. ADHD group showed significant delay in reaching this developmental marker. (*B*) Right lateral view of cortical regions of peak thickness by age (ages 7–13) in ADHD (*Upper*) and normals (*Lower*). (From Shaw et al. [71]).

ADHD and Underconnectivity: Its Relationship to Desynchronization

Cortical underconnectivity has been correlated in various neurodevelopmental and psychiatric disorders with desynchronization of large cortical networks. Dockstader et al. [89] note that convergent evidence from neurobiological studies of ADHD identifies dysfunction in fronto-striatal-cerebellar circuitry as the source of the behavioral deficits. They also note that recent studies have shown that regions governing basic somatosensory processing show abnormalities in those with ADHD suggesting those processes may also be compromised. In this study they used event-related magnetoencephalography (MEG) to examine patterns of cortical rhythms in the primary (SI) and secondary (SII) somatosensory cortices in response to median nerve stimulation, in 9 adults with ADHD and 10 healthy controls. Stimuli were brief (0.2 ms) non-painful electrical pulses presented to the median nerve in two counterbalanced conditions: unpredictable and predictable. They measured changes in strength, synchronicity, and in the frequency

of cortical rhythms. Their results showed that the normal controls showed strong event-related desynchronization and synchrony in SI and SII. By contrast, those with ADHD showed significantly weaker event-related desynchronization and event-related synchrony in the alpha (8–12 Hz) and beta (15–30 Hz) bands, respectively. This was most striking during random presentation of median nerve stimulation. Adults with ADHD showed significantly shorter duration of beta rebound in both SI and SII except for when the onset of the stimulus event could be predicted. In this case, the rhythmicity of SI (but not SII) in the ADHD group did not differ from that of controls. Their findings suggested that somatosensory processing is altered in individuals with ADHD.

The general assumption of cortical oscillations is that populations of neurons exist in varying states of synchrony as they respond to externally or internally generated events. Event-related desynchronous (ERD) and event- related synchronous (ERS) phenomena are thought to represent decreases and increases, respectively, in synchronization within a specific frequency range in relation to an event [90]. Previous MEG studies of cortical activity following median nerve stimulation in healthy adults report brief suppression of *mu* (an alpha wave variant oscillating at approximately 10 Hz) and beta (15–30 Hz) cortical activity over the primary and secondary somatosensory cortex (ERD) followed by a marked increase in beta band activity above baseline (late-ERS, known as beta rebound) [90]. Basic or complex sensory processing requires a dynamic interaction between groups of neurons oscillating at particular frequencies and differing degrees of coupling. Oscillations in the alpha and beta bands are of particular interest in ADHD research as these frequencies are thought to mediate perception [91, 92] and attention. [93, 94]

PATHOPHYSIOLOGY OF ADHD AND AUTISM: A COMBINATION OF GENETIC AND ENVIRONMENTAL FACTORS

The pathophysiology of ADHD remains unclear, although converging evidence suggests that alterations in brain structure, function, and physiology likely arise from an interaction of genetic and environmental causes and experience. [95-98] For example, structurally, prominent volumetric decreases are evident in the posterior-inferior lobules of the cerebellar vermis in both male and female children with ADHD [99]. There are decreases in prefrontal volume, particularly the right prefrontal cortex. [100] Also reported are regional differences in cerebral blood flow in the cerebellum, striatum, [101] and prefrontal cortex (PFC). [102] Moreover, differences in baseline oscillatory activity between those with ADHD and controls have been observed in frontal regions, particularly the PFC. [103] Consistent with the neuroimaging findings, psychological research indicates clearly that subtle impairing environmental problems are historical correlates of ADHD, regardless of gender or age. [104]

Epigentics and Autism

Schanen [105] indicated that many think that the autism spectrum disorders (ASD) that include autism, Asperger's disorder, childhood disintegrative disorder and pervasive developmental disorder-not otherwise specified (PDD-NOS) are largely genetic in origin, with a polygenic, epistatic model best fitting the family, twin and

epidemiological data for non-syndromic forms. The number of interacting loci contributing to susceptibility has been estimated to range between two and 15 genes of varying effect. [106] Despite considerable effort over the past decade, these underlying risk alleles have been remarkably elusive, with the exception of a handful of rare, large effect genes [107] and several single gene disorders associated with an increased risk for autism or ASD. [108]

Although this likely reflects the underlying genetic heterogeneity within and among the diagnostic categories in the ASD, the obstacles encountered in mapping the risk alleles have led a number of investigators to rethink the model of inheritance to include contributions of new mutations and/or epigenetic mechanisms such as genomic imprinting or epimutations in the underlying genetic susceptibility to ASD. [109, 110]

Epigenetic modifications including cytosine methylation and post-translational modification of histones provide a mechanism for modulation of gene expression that can be influenced by exposure to environmental factors and that may show parent of origin effects. Epigenetic effects can be related to sensory-motor based activity. Over the past two decades one of the most dramatic lifestyle changes has been related to early motor activity. Children at earlier and earlier ages have reduced motor activity and spatial exploration that is thought to be the single most important factor in gene expression and early synaptogenesis of functional connections in the developing brain. This can be compounded by the persistence of primitive reflexes and delay of postural reflexes which will further alter motor acquisition and spatial exploration.

Neurons can change their gene expression patterns according to the inputs they have received. This activity-dependent gene regulation mechanism plays an important role in the formation of neural circuits during development. Further, by regulating the synaptic plasticity, this mechanism may function as an essential one for each organism to adapt flexibly to its environment. Abe [111] summarizes the current knowledge about the activity-dependent gene regulation mechanism in neurons, focusing on the transcription factors and signaling pathways involved in this mechanism.

Epigenetics and Synaptogenesis

As we stated earlier primitive reflexes are necessary for early movement to occur in the absence of a fully formed neocortex. This movement allows for interaction and exploration of environment and basic survival behaviors such as feeding and approach and avoidance behavior. This interaction then engages the sensory receptors and activates the neural pathways which is thought to stimulate gene activity and synaptogenesis which creates neuroplasticity which will eventually lead to inhibition of primitive reflexes and the activation of postural reflexes. The postural reflexes then will engage the sensory systems, especially muscle spindle activation of postural muscles, which will then, through relevant feedback, create increasing synaptogenesis and neuroplasticity.

Flavell et al [112] have noted how sensory experience and the resulting synaptic activity within the brain are critical for the proper development of neural circuits. Experience-driven synaptic activity causes membrane depolarization and calcium influx into select neurons within a neural circuit, which in turn trigger a wide variety of cellular changes that alter the

synaptic connectivity within the neural circuit. One way in which calcium influx leads to the remodeling of synapses made by neurons is through the activation of new gene transcription. Recent studies have identified many of the signaling pathways that link neuronal activity to transcription, revealing both the transcription factors that mediate this process and the neuronal activity–regulated genes (a review in the context of enrichment is provided by Leisman in this issue [8]. These studies indicate that neuronal activity regulates a complex program of gene expression involved in many aspects of neuronal development, including dendritic branching, synapse maturation, and synapse elimination. Genetic mutations in several key regulators of activity-dependent transcription give rise to neurological disorders in humans, suggesting that future studies of this gene expression program will likely provide insight into the mechanisms by which the disruption of proper synapse development can give rise to a variety of neurological disorders.

As the neurons become larger and more insulated by glial cells, they increase the speed of their impulse transmission; more networks can be activated simultaneously increasing the coordination and integration of large cortical networks. Initially this increased coordination occurs with short range intracortical connections to increase integration and coherence within the individual hemispheres. As this coordination and synaptogenesis continues, long range connections will form and this will increase the size of the corpus callosum where many of these fibers will cross to connect with areas on the opposite hemisphere. This is all part of the normal process of cortical maturity. We think this is the process that is affected and delayed in most if not all neurobehavioral disorders.

Brain Maturation and Increases in Cortical Synchrony

Brain development is characterized by maturational processes that span the period from childhood through adolescence to adulthood, but little is known whether and how developmental processes differ during these phases. Uhlhaas and associates [113] have analyzed the development of functional networks by measuring neural synchrony in EEG recordings during a Gestalt perception task in participants ranging in age from 6 to 21 years. Until early adolescence, developmental improvements in cognitive performance were accompanied by increases in neural synchrony. This developmental phase was followed by an unexpected decrease in neural synchrony that occurred during late adolescence and was associated with reduced performance. After this period of destabilization, they observed a reorganization of synchronization patterns accompanied by pronounced increases in gamma-band power and in theta and beta phase synchrony. These findings provide evidence for the relationship between neural synchrony and late brain development that has important implications for the understanding of adolescence as a critical period of brain maturation [114].

Synchronization and Cortical Development

Recent data indicate that the synchronization of oscillatory activity is relevant for the development of cortical circuits as demonstrated by the involvement of neural synchrony in synaptic plasticity and changes in the frequency and synchronization of neural oscillations during development. Analyses of resting-state and task-related neural synchrony indicate that gamma-

oscillations emerge during early childhood and precise temporal coordination through neural synchrony continues to mature until early adulthood. The late maturation of neural synchrony is compatible with changes in the myelination of cortico-cortical connections and with late development of GABAergic neurotransmission. These findings highlight the role of neural synchrony for normal brain development as well as its potential importance for understanding neurodevelopmental disorders, such as autism spectrum disorders (ASDs) and schizophrenia. [115]

Oscillations and the generation of synchronized neuronal activity play a crucial role in the activity-dependent self-organization of developing networks. [116-118] The development and maturation of cortical networks critically depends on neuronal activity, whereby synchronized oscillations play an important role in the stabilization and pruning of connections [118]. For example, in spike-timing dependent plasticity, pre- and postsynaptic spiking within a critical window of tens of milliseconds has profound functional implications. [118] Stimulation at the depolarizing peak of the theta cycle in the hippocampus favors long-term potentiation, whereas stimulation in the trough causes depotentiation. [119] The same relationship holds for oscillations in the beta- and gamma- frequency range [120], indicating that oscillations provide a temporal structure that allows for precise alignment of the amplitude and temporal relations of presynaptic and postsynaptic activation that determine whether a strengthening or weakening of synaptic contacts occurs. Accordingly, the extensive modifications of synaptic connections during the development of cortical networks are critically dependent upon precise timing of neural activity.

Synchronization of oscillatory activity is an important index of the maturity and efficiency of cortical networks. Neural oscillations are an energy efficient mechanism for the coordination of distributed neural activity [115] that is functionally related to anatomical and physiological parameters that undergo significant changes during development. Thus, synchronization of oscillatory activity in the beta- and gamma-frequency range is dependent upon cortico-cortical connections that reciprocally link cells situated in the same cortical area, across different areas or even across the two hemispheres. [121] In addition to chemical synaptic transmission, direct electrotonic coupling through gap-junctions between inhibitory neurons also contributes to the temporal patterning of population activity and, in particular, to the precise synchronization of oscillatory activity. [122]

Gap-junctions are functionally important during early brain development. [123] Postnatally, changes in both GABAergic neurotransmission [124] and the myelination of long axonal tracts [125] occur. Thus, changes can be expected in the frequency and amplitude of oscillation as well as in the precision with which rhythmic activity can be synchronized over longer distances at different developmental stages. The literature on resting state activity as well as during cognitive tasks indicates that important changes occur in the parameters of neural synchrony during childhood and adolescence. Although high-frequency activity emerges during early development, cortical networks fully sustain precise synchrony only during the transition from adolescence to adulthood, which is compatible with concurrent changes in anatomy and physiology.

Csibra et al. [126] measured gamma band responses in EEG data in 6- and 8-months-old infants during the perception of

Kanisza squares that require the binding of contour elements into a coherent object representation. Based on prior behavioral studies that showed that infants up to six-months of age are unable to perceive Kanisza figures, the authors hypothesized that perceptual binding in 8-month-old infants is related to the emergence of gamma band oscillations. This was supported by an induced oscillatory response between 240 and 320 ms over frontal electrodes that was not present in the younger group, indicating that the emergence of gamma band oscillations during infancy is correlated with the maturation of perceptual functions. The development of induced oscillations and their synchronization was examined by Uhlhaas and associates [113,114,127] in a study that investigated children, adolescent, and young adult's perception of Mooney faces.

The data represented in Figure 3 indicated that in adult participants, perceptual organization of upright Mooney faces was associated with prominent gamma band oscillations over parietal electrodes as well as long-range synchronization in the theta and beta band. During development, profound changes in these parameters occurred that correlated with improved detection rates and reaction times

Accordingly, the development of induced oscillations and their synchronization from late adolescence to early adulthood reflect a critical develop-mental period that is associated with a rearrangement of functional networks and with an increase of the temporal precision and spatial focusing of neuronal interactions. Changes in neural synchrony during development are also present in the motor system in which beta band oscillations are associated with the preparation and execution of motor commands. [128] Synchrony of spinal inputs to motor neurons can be investigated by measuring the covariation of signals from electromygraphic (EMG) recordings over abductor muscles. Farmer et al. [129] analyzed the coherence of EMG-signals in the 1 to 45 Hz frequency range during development in a sample of 50 participants (4–59 years). Pronounced developmental changes in beta band coherence were found between 7–9 and 12–14 years, with adolescent participants showing elevated levels of beta band coherence relative to children.

In addition to the increase in the synchrony of EMG signals, there is evidence that long-range synchronization of oscillations between the primary motor cortex and muscles undergoes significant changes during development.

James and colleagues [130] examined EEG recordings over primary motor cortex and EMG data from the contralateral wrist extensor muscle in a sample of 48 participants (0–58 years). In the youngest age groups (0–3 and 4–10 years) coherence values between EEG and EMG signals were randomly distributed across different frequencies indicating that the drive from corticospinal pathways to motor- neurons is not oscillatory.

Uhlhaas et al [113], in a different study, reviewed evidence on developmental changes in neural synchrony during childhood and adolescence highlighting the relationship between brain maturation and changes in the frequency, amplitude and synchronization of neural oscillations. These data indicated that, in addition to providing a mechanism for the coordination of distributed neural responses that underlies cognitive and perceptual functions, neural synchrony is closely related to the development of cortical circuits.

This is indicated by the relationship between the emergence of specific patterns of oscillatory activity and certain cognitive functions and by the correlation between the

appearance of certain brain disorders at different developmental periods and electrographic signs of abnormal temporal coordination. Accordingly, such data support the view that neural synchrony is not epiphenomenal but plays a role in the functions of cortical networks.

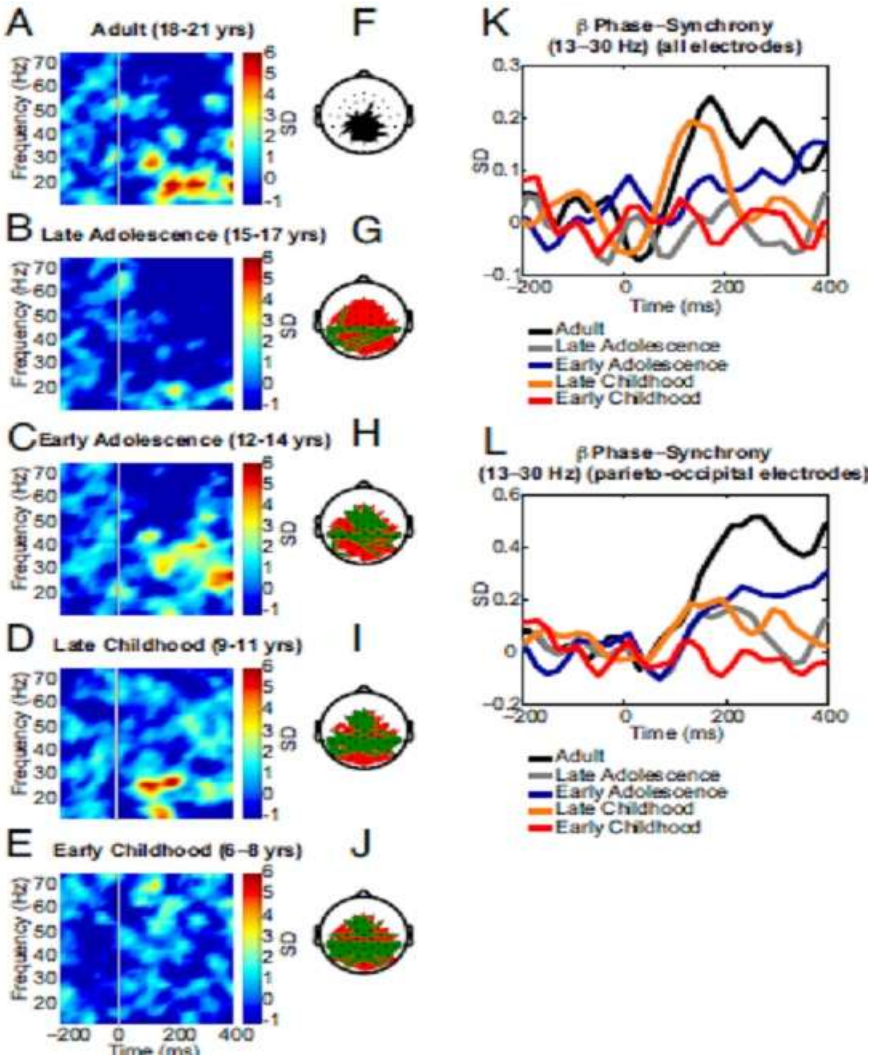

Figure 3. Phase synchrony in the beta and gamma bands in the Mooney face condition. All values are expressed in standard deviations in reference to the baseline. (Left) Phase synchrony (13–75 Hz) across all electrodes. (A–E) Adult (A); late adolescence (B); early adolescence (C); late childhood (D); early childhood (E). (Middle Column) Topography for 13–30 Hz frequency band between 100-300 ms. (F) Adult group. Synchrony between electrodes is indicated by black lines. (G–J) Difference maps for younger age groups relative to adult participants. Black lines indicate a significant increase (P _ 0.0003) in synchrony in adults compared with the younger group. Green lines indicate a significant increase (P _ 0.0003) in synchrony for the younger group relative to adults. (*K*) Group comparison for all electrodes of phase synchrony in the 13–30 Hz frequency range between 100 and 300 ms. (*L*) Group comparison for all parietooccipital electrodes in the 13–30 Hz frequency range between 100 and 300 ms. (From [130]).

Functional Disconnection as a Result of under connectivity, Desynchronization, and Poor Temporal Coherence and Immature Cortical Networks

We have proposed previously (for a complete overview see [16]) the concept of functional disconnection as a unifying model that can describe all of the symptoms and characteristics of the full spectrum of neurobehavioral disorders including ASD, ADHD, dyslexia, obsessive–compulsive disorder, Tourette's syndrome, nonverbal learning disability as well as possible relationships with other psychiatric disorders such as schizophrenia and bipolar disorder. Other authors have discussed similar mechanisms under different labels, desynchronization and underconnectivity [71], weak central coherence [131], temporal binding deficit [132], developmental disconnection, [133] and recently a new term, temporo-spatial processing disorders of multi-sensory flow and multi-system brain disconnectivity-dissynchrony. [see 131]

In their review [134], Gepner and Féron propose that temporo-spatial processing disorders (TSPDs) of multi-sensory flows represent a common neuropsychological basis for the main behavioral, cognitive and motor disturbances observed in people with ASD. According to this hypothesis, ASD individuals would present various degrees of disability in processing dynamic multi-sensory stimuli online, associating them into meaningful and coherent patterns, and producing real-time sensory-motor adjustments and motor outputs. We also present results demonstrating that slowing down the speed of facial and vocal events enhance imitative, verbal and cognitive abilities of some ASD children. Then, we propose that TSPDs are based on multi-system brain disconnectivity-dissynchrony (MBD), i.e. disorders of functional connectivity and neural synchrony within/between multiple brain regions, and review the recent fMRI and electrophysiological data supporting MBD. Finally, we list the suspected neurobiological mechanisms underlying TSPDs and MBD." All of these models essentially are all similar in where they focus on the inability of large cortical networks to bind in time and space. They note that the TSPD hypothesis emerged from data indicating that in ASD patients exhibit various degrees of disability in perceiving and integrating environmental dynamic multisensory stimuli online and producing real time sensory –motor coupling ,postural adjustments and adequate verbal and nonverbal outputs.

Autistic children have been shown to have weak postural reactivity to visually perceived environmental motion. [135] It has also been noted that children with low functioning autism are posturally hyporeactive to environmental movements especially when the speed of movement is high, whereas children with Asperger's syndrome display normal or even greater postural reactivity to the same type of stimuli. [136] It has been postulated that this under or over visuo-postural coupling in children with ASD may in part explain executive dysfunction in ASD patients [137] and sensory-motor, motor disturbances such as poor motor coordination, poor or enhanced postural control, gross or fine motor clumsiness. [138-142] It has also been shown that high functioning autistic subjects display a deficit in the perception of second order radial ,translational and rotational direction of movement [143].

ASD children also have difficultly perceiving the motion of small squares on a computer screen especially at high speed and when the direction was less predictable

[144] all implying a temporal processing deficit for particular types of stimuli. Other research supporting a temporal processing deficit comes from observed impairments in children and adolescents with ASD who were tested for their ability to extract online relevant information among noisy stimuli, through three types of tasks and measurements (a) occulomotor reactivity to global movements of coherent pattern of lighting points through optokinetic nystagmus, (b) speech flow perception and segmentation through categorization of simple and complex phonemes and (c) proprioception and motor anticipation in a bimanual load lifting task. [145] Results showed that the ASD subjects showed weak oculomotor reactivity in response to global motion (i.e. higher motion coherence thresholds, when compared to controls. [146]

Weaker occulomotor reactivity was observed in reaction to higher motion velocities [146]. It was speculated that this deficit which was assessed as a defect in rapid temporal analysis of visual motion stimuli embedded in noise is a strong argument for a deficient temporo-spatial integration in the visual modality. It is also thought that this difficulty to integrate single points into a global coherent motion is also the argument used for weak central coherence [146]. In the auditory realm, similar temporal processing deficits have been documented for rapid auditory processing. In a group of ASD patients they were shown to have a deficit in speech phoneme categorization. Compared to control children, who categorize ambiguous phonemes such as MNA in an MA or a NA random response, autistic children over categorize MNA in a NA response. This abnormal over–catagorization specifically appeared in autistic subjects when speech phonemes were displayed at normal speed, whereas their phoneme categorization was normalized when phonemes were slowed down by a factor of 2. It was speculated that phoneme categorization deficit may be due in part to a difficulty in rapid speech flow processing and therefore to a temporal integration deficit in the auditory modality. [147] This is thought to in part explain the receptive and expressive language and verbal communication deficits noted in individuals with ASD especially noting that the same deficit was found in children with Language learning impairments [148] and was improved by slowing down the speed of speech flow. [149,150]

Researchers think that deficient rapid temporal processing may contribute to impaired language development by interfering with the processing of brief acoustic transitions, critical for speech perception. It was also shown that in the rapid processing of proprioceptive inputs [151] autistic children mostly use a feedback mode of control as opposed to feed forward in normal controls. This results in a slowing of the movement of autistic children. Autistic children react instead of predicting. It is thought that this impairment along with the visual-proprioceptive processing deficit (i.e. deficit of visual-postural and visuo-occulomotor reactivity), contribute to executive dysfunction in ASD individuals and particularly to slowed sensory-motor processing speed. This could also be viewed as immature processing of particular information relative to the performance of non-impaired children of the same age. It was found that ASD individuals who perform poorly in facial recognition tasks involving processing of facial dynamics, [152] perform equally as well as typical developing children of the same developmental age in emotional and facial speech recognition tasks when the stimuli are slowed down. [153]

Gepner and Féron [134] note that In regard to motor development, babies who

will later exhibit typical autism [153] or Asperger syndrome [154] show disturbances in some or all of the milestones of development, including lying, righting, sitting, crawling and walking. In addition, Adrien and associates [155] and Sauvage [156] observed that they frequently exhibit deficits of postural adjustment, a lack or a delay in anticipating attitudes as well as in oculo-manual coordination, all of these symptoms being possibly due to a distorted proprioceptive and visuo-postural integration, and stereotyped behaviors like swinging, rocking and swaying, possibly aimed at compensating it.

The time course of autistic symptoms during infancy may appear as succession and intrication of maldevelopmental cascades, in which early temporo-spatial processing disorders of visual, auditory and proprioceptive stimuli impact secondarily on (a) sensory-motor development, (b) verbal and emotional communication and social interactions between an infant and his physical and human environment. [156] One of these maldevelopmental consequences has been named E-Motion Mis-sight, i.e. various degrees of disability in perceiving and integrating motional and emotional stimuli on time. [157] E-Motion Mis-sight has been proposed to be an early precursor of mindblindness [158] and empathizing deficit. [158]

In summary, TSPDs of multi-sensory stimuli may account for numerous clinical and neuropsychological findings in ASD. The cerebellum [160] is known to play a crucial role in all these stages. First, visual inputs, especially dynamic ones, travel through mossy fibers via the pontine nuclei before reaching the cerebellum [160]. Second, the cerebellum plays a major role in speed and temporal coding and therefore in integrating multi-sensory dynamic inputs. [161] Thirdly, the cerebellum exerts a real-time fine tuning of movement. [162] Fourthly, the cerebellum contributes with the basal ganglia to motor control as well as to learning, [163] via projections on motor and premotor cortices as well as on prefrontal, temporal and parietal cortices. Yet, some of the most consistent neuroanatomic anomalies affecting people with ASD are likely to affect the cerebellum. [164] Visuo-cerebellar pathways, among other sensory-cerebellar pathways, are therefore highly suspected to be involved in the neurophysio-pathology of ASD, [165] that could explain the unusual visuo-motor reactivity and, possibly, the bizarre cognitive style and higher order cognitive peculiarities observed in these individuals.

Numerous investigators have linked the neuroanatomic abnormalities of the cerebellum with cognitive impairments in ASD, supporting the notion that disturbances in the inferior olive found in autism, [166-168] and consequently in olivo-cerebellar pathways, would disrupt the ability of inferior olive neurons to become electrically synchronized and generate coherent rhythmic output. These anomalies of synchronization would (a) impair the ability of individuals with ASD to process rapid information (e.g. their ability to use rapid sequences of cues for the development of normal language skills), and (b) result in slowing their perceptual and cognitive processing speed. Rapid received sensory information (rapid sensory flows) would arrive too quickly to be processed on time by the autistic brain. Appropriately, a neuromimetic model (i.e. a mathematic model simulating brain functioning) of brain connectivity found that the speed of synchronization depends on the dynamical and network parameters, and is most probably limited by the network connectivity. [169] Functional connectivity is the mechanism allowing the achievement of a cognitive task or perceptual process by coordinating and spatio-temporally

correlating activities between different neural assemblies. [170] Studies using functional magnetic resonance imaging (fMRI) during the past 5 years have confirmed that functional brain connectivity could either be decreased, [171, 172] or sometimes increased [173] in ASD individuals during either resting state and simple or complex cognitive tasks.

Asymmetric Development Leads to Underconnectivity, Desynchronization and Functional Disconnection

A global immaturity of the function of cortical networks in childhood would be associated with a reduction in motor activity, spatial exploration, experience-dependent plasticity, persistent primitive reflexes, and delayed postural reflexes. A more specific imbalance in maturity would be expected if there was an asymmetric development of primitive reflexes. If there existed unilateral persistence of primitive reflexes and unilateral delay of postural reflexes, we would expect an asymmetric development and maturity of the brain and nervous system.

Futagi et al [174] examined the relationship between asymmetry in the plantar grasp response during infancy. They reviewed the neurologic outcomes of 61 children with asymmetric plantar grasp responses during infancy during a follow up period of 2.8 – 11.9 years. All children had perinatal risk factors and/or neurologic signs except for asymmetric plantar grasp responses recorded during infancy. The outcomes consisted of cerebral palsy in 38, delayed motor development in 6, mental retardation in 3, borderline intelligence in 9, and normal in 5. Most patients demonstrated concordance between side of abnormal response, laterality in motor function, and abnormal CT findings. The asymmetry they observed in the plantar grasp response strongly suggested the existence of brain dysfunction. This study showed that a relationship between asymmetric development of primitive reflexes is related to persistence of motor abnormalities related to the same side. As we stated earlier, the plantar response is thought to be one of the reflexes that is most related to brain development whether due to injury or functional developmental delays. This type of asymmetrical development of the developing brain is something that has been very commonly seen and noted in almost all neurobehavioral disorders, especially ADHD, autism, Tourette's and dyslexia. Along with anatomical asymmetries there have also been functional asymmetries noted with "unevenness" of skills characteristic of all of these disorders, to varying degrees.

One of the most interesting features of those with neurobehavioral disorders is the "unevenness" of cognitive abilities. We have proposed elsewhere [8,175] 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 dyslexics [176]. Functional asymmetry within widespread cortical networks could result in decreased temporal coherence in certain networks while also resulting in enhanced temporal coherence in other functional networks. [177] 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.

Optimized brain function implies more efficient neural processing than non-optimized. One might expect optimized performance to correlate with more activity.

For the cerebral cortex the contrary seems to be the case: higher performance in several tasks has been noted, including verbal, [178] numeric, figural, and spatial reasoning, [179, 180] is associated with reduced consumption of energy in several cortical areas. This phenomenon has also been studied with EEG techniques in different frequency bands. The amount of a background power (7.5–12.5 Hz) decreases during cognitive activity compared with a resting state (event-related desynchronization, ERD); this decrease has been observed to correlate with higher performance in subjects with higher IQ scores [181, 182] or with higher performance after training, indicating a more efficient processing strategy for a cognitive tasks. [183] Yet the issues should include not only the expenditure of energy but also the nature of the functional connectivities between brain regions.

Associated with these functional asymmetries or imbalances also seem to be anatomical asymmetries noted only in these individuals and not in others that seem to mirror the functional imbalances. [177] Physically smaller areas of activation have been found consistently in various areas of the brain in individuals 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 [8, 16] There has also been noted reduced connectivity between various areas of the brain in individuals with autism and other neurobehavioral disorders. [8, 16, 184, 185]

The most significant reduction of cortical connectivity appears to be in the corpus callosum. [186] 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 think 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 within hemisphere coherence. [184] We have also reported reduced connectivity and coherence observed in the longer interhemispheric connections with increased connectivity and coherence with shorter intrahemispheric connections [184. 185] that we theorize leads to the enhanced capabilities such as those seen in savantism.

In Autism it seems that reduced coherence as well as connectivity is associated with underactivation 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. [8, 187] This hyper-dopamine activity is also associated with an enhanced function of the left hemisphere that has a greater concentration of dopamine [188]. Dopamine, the most widely studied of all neurotransmitters, is thought to play a crucial role in motivation [189] and higher-order intelligence [190] and in most major clinical disorders—including attention-deficit/hyperactivity disorder (ADHD), [191] autism, [8, 187] bipolar disorder (especially its manic phase), [192] obsessive-compulsive disorder (OCD), [193] Parkinson's disease, [194], schizophrenia, [195] and Tourette's syndrome. [196] Most of these hyperdopaminergic disorders show a very high co-morbidity [197] and many disorders besides autism have shown varying degrees of increased incidence in recent decades. [198]

We think that this asymmetric development of primitive and postural reflexes is associated with the asymmetric

activation of genes responsible for synaptogenesis especially of the long range connections between the two hemispheres. This, in turn, is associated with an underconnectivity and a desynchronization of large cortical networks. All are related ultimately producing a functional disconnection between brain regions.

Primitive Reflexes are Biomarkers and a Target of Treatment

The persistence of primitive reflexes may actually be one of the earliest markers of abnormal or delayed cortical maturation and by extension of neurobehavioral disorders. The rooting and sucking reflexes as well as many other primitive reflexes are present at birth. The inability to latch on and breast feed, which is often seen in children with developmental delays, as well as delays or asymmetry of rolling over at 3-5 months of age may be the earliest signs of autistic, ADHD as well as other neurodevelopmental delays. There are various therapists who recommend specific exercises that are thought to stimulate or reproduce primitive reflexes as a way of remediating various neurobehavioral disorders. Although the mechanism of how these exercises inhibit these reflexes and affect or improve neurobehavioral disorders has not been previously described to our knowledge. We speculate that utilizing these reflexes increases the sensory stimulation and feedback to the nervous system that stimulates genes responsible for synaptogenesis and neuroplasticity of more rostral and complex areas of the brain. This is associated with inhibition through descending propriospinal connections that inhibit these reflexes that would under normal circumstances lead to more complex individualized volitional control of movement that will stimulate growth and cortical maturity.

CONCLUSION

The persistence of primitive reflexes through childhood and adulthood has been associated with brain injury and various developmental disorders. They have also been documented in a number of functional neurological disorders of childhood that are not associated with any specific neurological insult or pathology. We think that the presence of persistent primitive reflexes is representative of a maturational delay which is also reflected in structural and functional changes and various motor and cognitive delays. ADHD, autism and most neurobehavioral disorders are increasing at epidemic levels and we think that the driving force behind this increase is a combination of genetic and environmental factors with the emphasis being on environmental factors. The most significant epigenetic factors we think relate to lifestyle changes over the past two decades especially reduction of early motor activity and spatial exploration of children. We think that this reduces the activation of activity and experience dependent genes that stimulate synaptogenesis and neuronal plasticity of central neurons and glial cells that help to build and increase the size and complexity of the brain during the especially the first 3 years of life. This is the basis we think of both the maturational cortical delay that has been identified in almost all neurobehavioral disorders and also the basis of the persistent primitive reflexes.

Normally after the first few months of life, the feedback created by primitive reflexes generated movement leads ultimately to the inhibition of these reflexes and to the activation of more complex

subsequent postural reflexes, resulting in a more complex interaction with the environment, that in turn leads to greater sensory feedback thereby activating genes that allow for the creation of integration and coordination between various cortical networks. As these cortical networks become more connected and integrated they increase the speed of their interaction and their synchronization improves allowing more areas to be activated simultaneously. If cortical maturity and motor coordination are delayed, which may happen as a result of the abnormal persistence of primitive reflexes, the brain will not continue to grow and develop at a normal rate thereby delaying the emergence of its more mature functions. Since the brain's hemispheres develop at different rates and at different times, with the abnormal asymmetric persistence of primitive reflexes a maturational imbalance can be produced where one hemisphere may mature at a normal rate while the other may be delayed in its maturity. This can create large imbalances in synchronization and temporal coherence decreasing the ability for large cortical networks between the two hemispheres from binding in time and space. This can result in a functional disconnection syndrome which can present with varied symptoms depending on the time, hemisphere and degree of the maturational delay and imbalance.

In conclusion, we hypothesize that most neurobehavioral disorders of childhood are a result of maturational delays and imbalances and not a result of actual structural damage or pathology, that they are primarily a result of environmental influences, and are therefore amenable to remediation. We think that the presence of persistent primitive reflexes and the developmental milestones that might be delayed or absent as a result of those reflexes may be the earliest markers of developmentally delayed children and also can be a target of early intervention along with multimodal hemispheric specific intervention.

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