Electrophysiological variants correlated with neurodevelopmental delays: A systems biology approach

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Abstract

The impact of electrophysiological variants affecting the systemic organization of brain functions, especially perceptual, cognitive, and behavioral functions, has been largely undocumented. Health and education concerns, advanced technology, and current neuroscience research, including neuropsychological/brain-behavior studies, have afforded us an increased understanding of the cerebral organization and psychological structure of human mental processes. This article takes a Systems Biology approach to the brain as a functional system. The cerebral organization/psychological structure of intelligence and learning is discussed, encompassing a working brain relationship among attention, perception, executive function, memory, speech/language, sensory/motor, and mood/thought functions. A summary of 50 case studies revealing the clinical correlation of the functional brain-behavior impact with electrophysiological variants is examined. Patient histories reveal a variety of conditions associated with neurodevelopmental delay, including attention deficit disorders, autism, dyslexia and related learning disorders, sensory/motor disorders, mood disorders, and language disorders. This impact emphasizes the need for more specific identification and treatment of this subgroup of individuals experiencing electrophysiological disturbances affecting their development and learning. Health and education implications are discussed underscoring the importance of collaboration among neuroscience, education, and health policy professions, aiding the quality of life of those affected.

Keywords: electrophysiological variants, Systems Biology, cerebral organization, “functions of intelligence”, neurodevelopmental delay, functional analysis, health/educational implications

1. Introduction

Advances in anatomic, imaging, electrophysiological and neuropsychological studies of the cerebral organization and psychological structure of human mental processes and development have allowed us to take a closer look at the cognitive and behavioral effects of electrophysiological variants in children. A Systems Biology approach addresses the brain as a functional system and advances a neuroscience understanding of the functions of intelligence/development, dependent upon nature and nurture: biophysiological and environmental cues. This specialty area needs continued inquiry, research, and collaboration among neuroscience, education, and health policy professions. It is a promising area in servicing children having neurodevelopmental delays and guiding their quality of life.

2. Timing

Time is a universal process that marks all biological and behavioral processes. Cognitive and behavioral processes require electrophysiological timing: a regulated synchrony of excitation-inhibition among neurons (brain cells) communicating with each other in short bursts of electrical currents, an action potential.

Neurodevelopmental Delay is associated with inefficient regulation/synchrony. In the past, this electrophysiological-behavioral link was not often addressed. In neuroscience, we see many children experiencing developmental delays whose electroencephalograms (EEG) reveal variants. This has been difficult to quantify. Electroencephalography uses a microelectrode to read the firings of a single activated neuron. The neuronal current that the electrode is recording is only one of approximately 100 billion circuits in the brain. Scope, therefore, has been a major problem. Unfortunately, the electrophysiological-behavioral link was dismissed and the focus was on clinical events (seizures) and repeated seizures (epilepsy) because these events were quantifiable.

Specialized neuropsychological/brain-behavior studies and advances in electroencephalography have allowed us to take a closer look at the brain-behavior link and widen the scope. We now have more quantifiable measures and more specific functional analysis for clinical correlation. Attending to this clinical correlation as reflected in the following studies, has resulted in more specific differential diagnosis and intervention. These interventions develop more efficient timing/regulation of the excitation-inhibition of neuronal connections, aiding neurodevelopment.

3. Measures of neuronal activity

The most often utilized technology/studies of this brain-behavior connection include

- Sleep deprived EEG and extended ambulatory EEG: electrical activity recorded from the scalp. Video monitoring is often used.
- Evoked potentials: presents stimulus and measures interval between presentation and reaction to the stimulus. Sensory stimuli: 30 - 50 milliseconds reaction after onset of stimuli. Complex stimuli: 150 - 250 milliseconds

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reaction after onset of stimuli. Cognitive stimuli: 300 milliseconds reaction after onset of stimuli.

- MEG: Magnetoencephalography: measures magnetic field of neuronal activity. Magnetic fields pass through the skull bone yielding more accurate findings.
- MRI: Magnetic Resonance Imaging: 3-D picture measuring strength of magnetic field viewing structure of the brain.
- fMRI: Functional Magnetic Resonance Imaging: measures strength of magnetic field while performing certain tasks.
- PET: Positron Emission Tomography: maps blood flow/energy used in the brain
- Neuropsychological Evaluation: provides a functional analysis of the cerebral organization and psychological structure of human mental processes and provides clinical correlation with other neuroscience studies.

Advances in these technologies and neuropsychological assessment have fostered more specific interdisciplinary differential diagnosis and more specific treatment.

4. The working brain

A Systems Biology approach toward understanding neurodevelopment views the brain as one of the most complex systems of nature/nurture. It is important to understand neurodevelopment, not just in terms of individual gene(s) or protein(s), but also in terms of functional systems and interactions in which the brain's genes/proteins operate, and the dependency upon environmental/external cues. Systems Biology addresses the working relationship among multiple brain systems, governing the cerebral organization and psychological structure of mental processes. This approach addresses the interplay among the systems incorporating neuronal pathways of activation and regulation (subcortical diencephalic/limbic formations), reception, analysis, and storage pathways (posterior brain), and expression/planning pathways (anterior brain areas). These systems are dependent upon biophysiological and environmental influences: nature and nurture. As the brain is being 'wired', multisensory connections throughout these systems of attention, reception, storage, expression, and planning are being excited and inhibited, guiding learning and development. Efficient synchrony and modulation of this excitation and inhibition of stimuli guides the brain-behavior relationship. At young ages, lower brain systems influence higher cortical brain systems. As we develop, higher systems influence the lower systems. This 'working brain' relationship strengthens learning and development. The brain is the only organ in the human system that learns.

5. Wiring the brain

In utero, neurons proliferate widely making connections ready for a lifetime of experiences. Neurons develop axons (send signals) which have multiple branches to other neurons and dendrites (receive signals). The growth cone of the axon searches for proteins encoded by genes. Some proteins attract the growth cones and others repel them. These biochemical sources of neurons have electrical magnetic fields. Electromagnetic bursts excite/inhibit connections among neurons. Synchronization between exhibition/inhibition guides the brain's timing, like an inner clock, setting the pace for a developmental journey, dependent upon nature (genetic makeup) and nurture (multi-sensory experiences from the environment). At 3 weeks, cells in the neural tube grow at approximately 250,000 per minute and the brain/spinal cord develops. At 6 weeks, the embryo's brain is almost as big as its body. At birth, the brain experiences a growth spurt at which time axons and dendrites explode. Electrochemical activity, dependent upon sensory experiences and genetic makeup, fine tunes these connections. Some connections are excited and some are inhibited. A melody of synchrony among multibrain systems continues, advancing development and learning. There is much to learn about the magic of these biochemical, electrophysiological, and neuropsychological processes. Neuroscience is gaining continued understanding of the brain-behavior relationship.

5.1 Wiring Attention

Deep and central parts of the brain (subcortical, diencephalic/limbic pathways) are among the first circuits to develop. Vital metabolic functions and behavioral functions, generated by these attention pathways, are excited/inhibited by nature and nurture influences. In sleep states, attention connections are more inhibited. In wake states, attention connections are more excited. At birth, infants are faced with an explosion of multisensory stimuli, no longer solely dependent upon the influences of the womb. As a child develops, learning to attend and focus upon necessary stimuli, these lower brain areas build connections with higher brain areas (cortical areas) exciting/inhibiting attention pathways throughout the brain. This is referred to as higher cortical attention processing. Efficient neurodevelopment requires efficient synchrony, regulated modulation of excitation-inhibition, of neuronal connections within these attention pathways.

5.2 Wiring the mood

At birth, the infant is protected by startle reflexes allowing the infant to cope with the explosion of sensory experiences from the environment. These startle reflexes develop synchrony and modulation through biophysiological and environmental influences, aiding the child in controlling feelings and developing emotion. Relaxed alertness is necessary for optimal development. Efficient synchrony and regulated modulation of mood significantly influences multisensory pathways throughout the brain.

5.3 Wiring movement

Infants are born a bundle of sensory-motor reflexes. Throughout development, these reflexes become more controlled and refined movements develop, allowing for sucking, grasping, sitting, crawling, walking, climbing, handwriting, coloring, and enhancing development of higher level cognitive and behavioral functions. Biophysiological and environmental influences govern sensory-motor development. Efficient synchrony and regulated modulation of movement pathways is necessary for healthy development.

5.4 Wiring Vision

Infants can see at birth. Biophysiological and environmental influences govern visual connections in the brain allowing for development of focusing both eyes and the more highly developed functions of visual perception. The connections among head and neck movements, body movements, and eye movements aid in multiple functions of visual learning, aiding in development of higher cortical visual processing.

5.5 Wiring speech and language

Melody of voice, especially a mother's voice, is sensed in utero. Efficient synchrony/regulated modulations of sounds is governed by biophysiological and environmental influences. At 6 months, infants especially recognize sounds of speech of their native tongue and have difficulty with sounds other than their native tongue. This melody of sound within auditory brain pathways is highly associated with movement pathways. Movement produces vibration which produces sound. Visual pathways chime in connecting objects with sounds and words. Mood pathways are also associated with sound. The harmony of the working relationship among these systems aids in developing higher cortical auditory pathways and speech/language development.

5.6 Wiring memory

Memory is an active and complex task requiring a working relationship of multiple brain systems. Efficient biophysiological and environmental excitation-inhibition of stimuli is needed to develop memory traces. 'Working memory', the interplay and consolidation of memory traces, is dependent upon efficient synchrony and regulated modulation of multisensory stimuli. Consolidation of memory traces guides self-direction and executive function-planning abilities. This modulation guides the process of habituation, the cessation of orienting-attention reflexes, responding to stimuli, aiding memory consolidation. In young childhood, memory processes and learning require repetition. As we grow, we learn and develop continued memory traces by recollection and reflection. Memory consolidation affects all aspects of human behavior and learning.

6. Electropysiological – behavioral link

We have discussed that the brain-behavior link regarding electrophysiological variants and Neurodevelopmental Delay has only recently received more attention.

The current literature reviews tend to focus upon pervasive developmental delays associated with electrophysiological variants, largely because the behavioral impact increases with more wide spread neurophysiological disturbance. A very recent publication cited "a retrospective review of 24 hour ambulatory digital EEG data collected from 889 autistic spectrum disorder patients presenting between 1996 and 2005, with no known genetic conditions, brain malformations, prior medication, or clinical seizures. It showed that 540 of 889 (60.7%) subjects had abnormal EEG epileptiform activity in sleep with no difference based on clinical regression. The most frequent sites of epileptiform abnormalities were localized over the right temporal region. Of 176 patients treated with valproic acid, 80 normalized on EEG and 30 more showed EEG improvement compared with the first EEG (average of 10.1 months to repeat EEG) [1]. The authors in this study encouraged early screening of individuals with autistic spectrum disorders using prolonged sleep electroencephalograms in order to assess the presence of subclinical epileptiform activity and better understand autism and the brain behavior relationship.

The following older (1998), yet pertinent example, demonstrates the brain behavior relationship in a child diagnosed with Landau-Kleffner Syndrome (epileptic aphasia/language disorder) which was presented through *Case of the Month--DigiTrace EEG Lab* by this author [2].

Case History: "This is a 6-year -old male who presented at age four years with a symptom complex correlated with Atypical Pervasive Developmental Disorder. The most salient symptoms were inattention, marked speech and language delays and heightened lability of mood. Expressive language was described as "almost mute, giving one word responses at times." Socially, he was described as playful, but displayed little fluent interaction. There was no history of an acquired neurological illness or injury. Birth and neonatal period were unremarkable. At age four years, a sleep deprived EEG and MRI were unremarkable. Intelligence tests revealed a Verbal IQ of 65, (intellectual deficient), Performance/non-verbal IQ of 70, (borderline) and a Full Scale IQ of 65, (intellectually deficient.) Developmental tests of verbal, non-verbal and social interaction skills revealed less than 2 year 5 month range. Fragile X chromosome testing was negative. Stimulant medication produced tic symptoms. Antidepressant medication improved impulse control. At 4 years 10 months, heightened inattention and a regression of language functions were evidenced. Monitoring was initiated to investigate these changes."

Clinical Interpretation: "During a 24-hour EEG monitoring, two push-button events were recorded which did not show any epileptiform activity. Five seizure files were also recorded showing frontal sharp waves and generalized sharp slow wave activity with right sided predominance. Eight pages of spike files were recorded revealing high amplitude sharp waves in the right frontal region."

Continued Treatment: "This electrophysiological finding, coupled with the regression of functions, prompted a trial of antiepileptic medication in conjunction with continued antidepressant medication. Clinical response was quite positive. It was the first time complete sentences were heard (I.e.: "what are we going to do today?"), preservative responses lessened and play increased. Approximately one year later, a second 24-hour EEG test was initiated. Monitoring appeared normal. The patient continues to have improved attention, non-verbal and organizational skills, social interaction and impulse control. Verbal skills continue to increase, yet at a slower pace. Non-verbal IQ scores have increased 15 points (85: below average/average). Verbal IQ scores increased by 6 points (71: borderline). Full Scale IQ increased 11 points (76: borderline/below average). Non-verbal developmental tests increased from less than 2 years 5 months (1995) to 5 years 5 months--7 years 5 months (1997). Test of verbal skills increased from less than 2 years 5 months (1995) to 3 years--4 years 8 months (1997). Social interaction/social awareness tests increased from less than 2 years 5 months (1995) to 5 years 5 months (1997)."

This case study highlighted the critical importance of early age identification and treatment of children having Neurodevelopmental Delay, especially pervasive developmental disorders, using prolonged sleep electroencephalograms and neuropsychological evaluation providing functional analysis/ clinical correlation of the brain-behavior relationship.

The Brain: Behavior relationship: Electrophysiological-Behavioral Clinical Correlation: A Summary of 50 Case Studies

This summary highlights a random review of neuropsychological assessments of 50 children evaluated by this author. The children's folders were earmarked to note that the neuropsychological studies were clinically correlated with electrophysiological data revealing variants. The children ranged from ages 2 years to 10 years of age.

Table 1. Child's age and number of children in study

Child age (Years)	Number of children in study
2	1
3	2
4	5
5	11
6	8
7	11
8	5
9	6
10	1

Table 2. The children presented with various diagnoses

Diagnosis	Number of children
Cerebral Palsy	2
Intractable Seizure/hemispherectomy	1
Arteriovenous malformation	1
Hemiparesis	2
PDD	12
Autistic Regression	3
ADD/LD	29

Table 3. Imaging studies

Revealed from imaging studies	Number of children
Abnormal visual evoked potential	1
Prominent lateral ventrical	3
Dilation of temporal horn of right lateral ventrical	1
Prominent cisterna magna	2
Widening of diploic space-parietal	1
Cavum septum pellucidum deformity	3

Table 4. Generalized electrophysiological disturbances

24 children: generalized spike-wave discharges
5 children: <u>continuous</u> spike-wave discharges in sleep:
Predominance in:
- Right frontal temporal
- Left temporal
- Left temporal central
- Bilateral temporal
- Right temporal central

5 children: generalized slowing

Table 5. Focal electrophysiological disturbances

8 Left temporal
9 Bitemporal
2 Left anterior temporal
6 Right temporal
4 Left frontal, frontal-temporal
2 Right frontal temporal
1 Left frontal temporal
1 Right central temporal
2 Left occipital
3 Right occipital
5 Left central
4 Right central
5 Right frontal

Neuropsychological evaluations of all of the children revealed central nervous system disturbances and demonstrated neurobehavioral symptom complexes, correlated with the electrophysiological variants.

Intelligence (IQ) Summary

A review of IQ scores revealed a globally average bell curve. Note that 12 of the children experienced a neurobehavioral symptom complex in the presence of above average - very superior/gifted intelligence. (Note: Average IQ range: 90-109)

Table 6. IQ summary

Very Superior	3
Superior	5
Above average	4
Average	15
Below average	7
Borderline	5
Mid deficiency	5
Moderate deficiency	2
No formal IQ	4

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Table 7. IQ Examples

Lowest Verbal IQ (VIQ)	46
Highest Verbal IQ	140
Lowest Performance IQ (PIQ)	66
Highest Performance IQ	130
Lowest Full Scale IQ (FIQ)	54
Highest Full Scale IQ	139
*Greater than 10 pt Verbal-Performance (non-verbal) discrepancy	23

*A pathognomonic sign of cerebral disturbance

Table 8. Case cxample—highest Verbal IQ

5-year-old who could not recall letters of the alphabet and presented with 8-month regression of language. EEG: Epileptic aphasia (language) disorder: Landau-Kleffner syndrome.

Verbal IQ	140
Performance IQ	126
Full IQ	139

Table 9. Case example—highest Performance (non-verbal) IQ

History of language regression and EEG consistent with epileptic aphasia. Sister's history is also remarkable for seizure disorder and a cousin with autism.

Performance IQ	130
Verbal IQ	100
Full IQ	115

Table 10. Case example: VIQ 46, PIQ 69, FIQ 54

6 year old child with autism and hyperlexia. Her fraternal twin died: history of placental infarct

Non verbal cognitive index	5.0 years
Expressive language index	2.3 years
Receptive language index	3.5 years
Social index	3.1 years
Motor index	4.2 years

Frequent staring episodes reported

EEG: sleep activated right temporal focus with generalization

Table 11. Case example: 25 pt V-P discrepancy in favor of verbal scale

VIQ 135 PIQ 110 FIQ 125

10 year old with history decreased left-sided motor skills. EEG revealed generalized paroxysmal sharp activity in sleep.

Written expressive language	40%ile
Verbal Reasoning	90%ile

Frequent staring episodes coupled with dropping what he is holding

Table 12. Case example: 46 pt V-P discrepancy in favor of Performance IQ

VIQ 74 PIQ 120 FIQ 94

4 year old

Verbal language index	2.5 years
Nonverbal language index	6.5 years
Receptive vocabulary	2.1 years
Spontaneous expressive vocabulary	3.1 years
Demand expressive vocabulary	2.5 years

EEG: right frontal and bi-temporal sharp activity/ generalized activity in sleep and slow activity in these regions

Functional-Behavioral symptom complex:

Table 13. Attention/executive function

Hyperactivity	23
Hypoactivity	11
Distractibility	16
Staring/Daydreaming	17
Nocturnal enuresis	15
Sleepwalking	3
Rocking/head banging	4
Hand flap/swipe movement /repetitive behaviors	7
Perseverative/routine behaviors difficulty with transition	10

Sleep disturbances were very common, especially difficulty falling asleep, limb movements, nighttime awakening, and night terror.

Table 14. Sensory-motor

Drooling	2
Repetitive motor/phonic tics (i.e. eye blinking, nose sniffling, throat clearing, facial grimacing)	6
Hypotonia	11
Left hemiparesis	2
Fine and/or gross motor variance	17
Optic motor/tracking deficits	28
Decreased kinetic melody of movement	6
Sensory sensitivity/defensiveness	7

Table 15. Speech-language

Language regression (regression between ages 2 and 4 years)	5
Dysarthric speech	21
Hyperlexia	3
Stutter	1
Mute	1
Receptive and/or expressive language delays	37
Reading problems	38

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Table 16. Mood

Frustration/labile mood	50
Bipolar disorder	2
Obsessive-compulsive symptoms	4
Agression/temper	10
Asked to leave school prior to age 4	2
Sleep disturbance	22
Acute depression	15
Suicide attempt	1

Table 17. Memory

100% of the children presented with 'working memory' indices in impaired ranges. Well-consolidated memory/ long term memory traces were globally average or above in the majority of the children. Rapid prompting/rote memory traces were also globally average. Inefficient electrophysiological synchrony/modulation impedes habituation, the cessation of orienting-attention reflexes, and results in poor 'working memory' consolidation. Memory consolidation affects all aspects of human behavior and learning. Interestingly, several of the children commented, "I forget a lot", "I need a lot of repeating", "I can't remember what letters look like".

A qualitative view of the children's histories and patterns of performance indicated salient symptoms suggesting the need for an EEG study. These symptoms included sleep disturbances such as nighttime awakening, limb movements, sleepwalking, night terror, and nocturnal enuresis. Additional symptoms included staring episodes followed by slower reaction times, chronic inattention, chronic receptive, storage, and expressive disturbances of sensory-motor, memory, language, learning, and mood functions, and major IQ discrepancies, especially verbal scale--performance scale discrepancies greater than ten points.

Indicators suggesting the need for an EEG study can include, but are not limited to, pregnancy complications (i.e. low birth weight, pre-post mature delivery), trauma (i.e., infection, injury/traumatic stress), family history of seizure disorder, or regression of functions.

7. Conclusion

Neurodevelopmental Delay having multiple etiologies, can have a multi-functional systemic effect upon development and learning. We have addressed the clinical correlation between electrophysiological disturbances and neurodevelopment from a Systems Biology approach, emphasizing the brain as a functional system requiring the working relationship of multiple brain areas. Neuropsychological study of the Brain-Behavior relationship was described by this author in a 1985 clinical research study [3] which addressed neurodevelopment from this Systems Biology approach. Advances in technology and neuropsychological assessment have resulted in more specific functional analysis of the psychological structure and cerebral organization of human mental processes. This understanding of the brain-behavior relationship has aided in more specific differential diagnosis and more specific interdisciplinary treatment interventions.

Interdisciplinary therapeutic interventions targeted at developing functions of neurodevelopment and intelligence, influencing attention, perception, memory, executive function, speech/language, sensory/motor, and mood/thought functions, have both biophysiological and environmental impact. The brain is a dynamic system that learns. It is curious and compelling to address advances in neuronal development and neuroprotection which can influence genetic makeup.

The electrophysiological-behavioral link is a promising area which needs continued inquiry and research. It embraces a group of children with neurodevelopmental delays associated with electrophysiological variants, and promotes therapeutic interventions guiding their quality of life. Interdisciplinary evaluation and treatment must include collaboration among neuroscience, allied health, education, and health policy professions.

8. Education and health implications

Current brain research has enhanced our knowledge of child development, normal and abnormal development. Scientists such as Luria, Maslow, Erickson, Montessori and Piaget presented us with developmental theories based upon observed child development and/or neurological injuries. Scientists and educators referred to and incorporated their knowledge into a design of early childhood and educational approaches for years. We now know more about the scientific, neurobiological base for these theories. We know that environments that maximize the fullest brain development for all children increase brain synchrony/modulation and healthier brain development. Early, brain-appropriate, consistent intervention is essential for all children. The younger the child, the easier and more productive the efforts will be.

We are aware that lower brain attention and mood systems influence higher brain systems of attention, reception, memory, and expression/planning. We know that a synchronized brain functions and learns more easily. Due to advanced neurobiological/neuropsychological knowledge, we are aware that all classrooms need to be calm to allow for the greatest amount of synchrony. The opportunity for hands-on experience and movement with much repetition should be maximized. Environments with immersion into natural language and social exposure enhance the higher-level neuronal connections necessary to prepare children for higher cognitive learning at all developmental levels.

These research-based guidelines form the foundation from which adaptations for special needs children can be made. We know that the children in our study who had electrophysiological disorders presented with a full array of intelligence variables, some having above average and superior IQ scores. Many had been previously diagnosed with ADD/LD or PDD. Electrophysiological disturbances revealed generalized and/or focal patterns. Imaging studies also revealed some structural variances. The areas of disturbance were correlated with coexisting developmental/intellectual/affective symptoms. Functional-behavioral symptoms included hyperactivity, hypoactivity, staring, distractibility, nocturnal enuresis, and persevera-

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tive/routine--difficulty with transition, hand flapping, rocking, and sleepwalking. Many had reading problems, receptive and expressive language delays, and dysarthric speech. Many had optic motor/tracking difficulties, fine and gross motor variants, and hypotonia. Frustration/labile mood and memory related difficulties were universal symptoms. Sleep disturbance, acute depression and aggression were common.

It is important for educators to recognize possible symptoms of related electrophysiological/developmental/learning disorders, so they can alert parents when these behaviors are observed. As symptoms are recognized by informed, caring educators, parents can be alerted and proper health intervention initiated. Consistent health and education communication with parents enhances a fuller understanding of each child and can build a partnership of care. A responsive, caring environment can compensate for and assist in minimizing the amount of electrophysiolgical dyssynchrony, while increasing the level of learning/development in these vulnerable children.

Electrophysiological disturbances in any child can interfere with development through inefficient connections, erasing some connections, and scrambling others. Immature primitive reflexes can be the source of a full range of learning problems. Whether or not the underlying medical condition is identified, the child's subsequent development is being altered. Whether or not the neurobiological source of the interference is identified as seizure disorder, PDD, ADD/LD..., the learning environment must be adapted when symptoms are noted. Through informed careful observation, educators can alter teaching techniques to better match the identified learning patterns of the children. The symptoms do not have be identified as seizure-related but must call for adaptations because they exist as learning styles and/or impediments to the "functions of intelligence", learning, and development. Educational intervention in such a manner maximizes brain development, learning, the "functions of intelligence" and self-esteem in children. Children with electrophysiological disturbances need an especially responsive and gentle environment that maximizes their feeling of safety and calm. They need to experience relaxed alertness to help soothe their brain and maximize development. They need MUCH repetition to compensate for the confused internal message system due to incomplete, erased and/or scrambled connections, and allow for more consistent learning. Attending to the timing/synchrony of how multisensory stimuli is presented allows for more efficient reception, storage, and expression of stimuli. This eases attention, processing, and opportunities for repetition which aid consolidation of memory traces for recollection and reflection. For example, modulating the speed, tone, and volume of auditory stimuli, and modulating the presentation of visual and sensory motor stimuli, and modulating the presentation of visual and sensory motor stimuli, especially when the child is in a state of relaxed alertness, assists in development of the learning process. Learning the location of the seizures is not always necessary but can further pinpoint classroom interventions—language assistance, reading support, math clarification, writing assistance and/or social skills being taught directly. Interdisciplinary health, allied health, education, and policy intervention is necessary. Assistance should be given based on identified concerns rather than adherence to an IQ-achievement discrepancy or other numerical formulas. A full, daily organizational structure may be necessary to assure assignment completion in a timely fashion. These are children for whom assistance toward successful learning will change their brains, develop their intelligence, and change their futures. Health policy must view learning as a major health issue. The impact of our children's health and learning affects global societal health.

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