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24

Connecting Electroencephalography Profiles with the Gamma-Amino-Butyric Acid (GABA) Neuropathology of Autism as a Prelude to Treatment

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1. Introduction

The nervous system has the ability to adjust in the face of disease by reorganizing its molecular, cellular, and systems function for survival through the mechanism of neuroplasticity. Recently, the National Institutes of Health Blueprint for Neuroscience Research, USA, gathered experts in various fields of neural disorders to look into the translation of neuroplasticity and circuit retraining research: the message is that the future ahead is very bright for effective clinical therapies (Cramer et al., 2011). When research studies are driven by basic science conceived alongside therapeutic disciplines designed in a congruent manner, there is the exciting potential that the innate mechanism of neuroplasticity could be shaped more precisely and more thoughtfully than is currently available. The vision for the future is patient-centered therapy aimed at the rewiring of brain circuits for successful function with long term changes in the molecular and genetic level.

The transcriptional machinery is a site where neuropathology can occur. Alterations in gamma-amino-butyric acid (GABA) through transcriptional machinery may be one of the factors that underlie the neuropathology of autism. The level of transcription via the synthesizing enzymes for GABA plus the neuroplasticity response of interneurons in the brain will be discussed in this chapter. The implication on the afferent-efferent circuitry in the cerebellum with the promising application of a neuropathological understanding of autism to treatment and behavior will be presented.

Autism is not a single disease entity. It is often referred to as autism spectrum disorder (ASD). The condition is behaviorally defined, described, and diagnosed by a triad of deficits which include the following characteristics: impaired social interaction, impaired communication, restricted interests with stereotyped and/or repetitive behaviors. Another behavioral feature is sensory input sensitivity. Autistic individuals are hypersensitive to stimuli regarding sound, light, touch, smell, temperature, and pressure. These sensations can limit the individual's ability adapt to the regular noise and activity levels typically encountered in shopping malls, school classrooms, and other public gathering sites.

Additionally, the sensory overload severely affects one's ability to screen out noise and process relevant signals. This reactive hypersensitivity significantly impacts the family's lifestyle as each member has to adjust to the disease manifestations on a day-to-day basis. Paradoxically, sensitivity to pain (Tordjman et al., 1999) and the ability to be sedated (Marrosu et al., 1987) may be diminished in certain autistic individuals as there exist in certain subtypes, an alteration in pain and sedation neuroreceptors.

The behavioral features of autism remain a mystery. Kanner's (1943) original description of autism stated that it is a disorder of "nervousness". "Nervousness" is regarded as the staunch refusal of the autistic individual to change his or her routine in order to "go with the flow. This is a common behavior that caregivers have to grapple with routinely. Both parties become frustrated as a result of the emotional intensity that is generated. A favored treatment recommendation, recognized by the health system and the public, consists of behavior modification on the part of the autistic individual (i.e., the child).

To date, preferred treatments of the neurodevelopmental disorder defined as autism are the behaviorally-oriented refinements of ABA. However, there is a paucity of data linking behavior with its neurobiological correlates that could have caused the behavior. Behavior is the final product of a cascade of events beginning with genetic and transcriptional coding of genomic information to the culmination of neurochemical transmitters which intersect on neuronal circuits in the brain to finally give rise to behavior (Figure 1). It is necessary to link the multiple systems into a hierarchy of events so that a big picture could be constructed lest we become like the legend of "the blind men and the elephant", where a group of blind men were each feeling a different part the elephant and each man came up with a different description depending on the part of the elephant he has touched. In the case of autism, each researcher- through the lense of his or her discipline- feels one part of the puzzle and assumes that one or another represents the whole.

2. The neurotransmitter γ-Amino butyric acid (GABA)

This journey begins with a single neuro-transmitter. GABA is selected because considerable evidence points towards a hypothesis of GABA deficiency occurring in autism. For example, a reduced density of $GABA_A$ and benzodiazepine receptors in the hippocampus (Blatt et al., 2001), a reduction in the level for GABA synthesizing enzymes (GAD65 and GAD67) in the parietal and cerebellar cortex (Fatemi et al., 2002; Yip et al., 2007, 2008, 2009), and the effectiveness of the $GABA_A$ receptor agonists in treating seizure and anxiety disorders in autistic patients (Askalan et al., 2003; Acosta, 2004) reported in autistic patients all point towards a lowered GABAergic function. Genetic studies have found interstitial duplication in the chromosome 15q11.2-q13, a region containing three GABAA receptor subunits, in autism phenotypes (Schroer et al., 1998; Shao et al., 2003; Menold et al., 2001; Ashley-Koch et al., 2006).

The perturbation of GABA in autism can lead to neuropathological changes at a cellular level that resides in a particular circuit within the brain. The main components governing GABAergic neurotransmission lies in its two isoforms of synthesizing enzyme- glutamic acid decarboxylase (GAD), which are GAD65 and GAD67. GAD is the precursor through which GABA transmission is carried out. Results from our study implies that an *in vivo* cerebellar circuit of cell-type specific afferent-efferent network leads to a GABA neuropathological mechanism in autism that are likewise compensated through the same circuitry via GAD through neuroplasticity (Yip et al., 2007, 2008, 2009; Blatt et al., 2010).

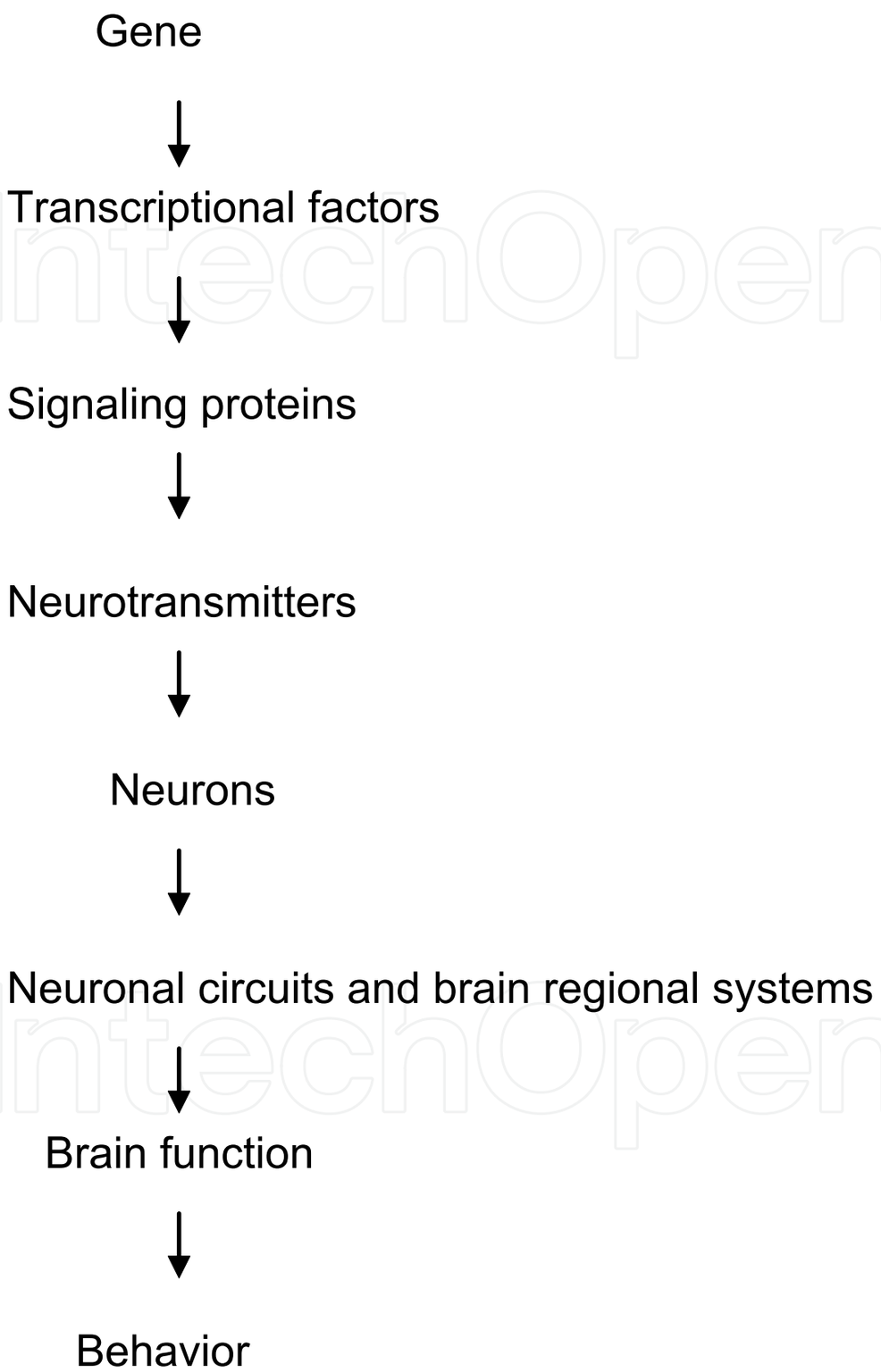


Fig. 1. The hierarchy of biological systems giving rise to behavior.

The next step is to extend the study GABA dysregulation to behavior. An autistic child often finds informational input, particularly sensory data, overwhelming. Autistic children have stated that they feel as if the physical world is too difficult or confusing to handle sometimes. In short, their comfort zone is disrupted. Since one of the major brain centers of sensory information processing is located in the cerebellar circuitry, its study is beneficial in order to identify the source of their confusion. Furthermore, it is necessary to correlate the child's brain function within one's natural environment (i.e., home, schools, clinician's office) as they relate various activity states such as resting, performing a mental task, and being subjected through a bombardment of sensory input that surrounds an autistic child on a daily basis. The authors propose that through a non-invasive portable method of testing one's brain function in the child's natural environment (i.e., *in situ*) such as the electroencephalography (EEG) technologies, the field of autism research and treatment could be further enhanced.

3. Physiological regulation requires glutamic acid decarboxylase synthesis

GABA is a bountiful inhibitory amino acid neurotransmitter catalyzed by the enzymatic action of GAD from glutamate. GAD activity is altered in many disease states such as stiff-person syndrome (Meinck et al., 2002), epilepsy (Vianello et al., 2002), and Parkinson's disease (Guridi et al., 1996).

GAD exists as two isoforms encoded by GAD65 and GAD67 that exist in mammals and are highly conserved. GAD67 is acted upon by coenzyme pyridoxal-5'-phosphate (Martin et al., 1991; Martin and Rimvall, 1993) for the synthesis of GABA via ribonucleic acid (RNA) regulation whereas GAD65 is constituitively expressed by a promoter regulated by coenzyme-saturation (Rimvall et al., 1993). GAD65 is considered to be mainly involved in regulated GABA synthesis. These two GAD isoforms presumably originated in vertebrates following gene duplication approximately 450 million years ago before the emergence of sharks and rays (Lariviere et al., 2002) and differ in subcellular distribution and have different roles in the regulation of GABA. The relative amounts of the isoforms expressed may reflect the functional adaptations of that particular cell. There is a third novel form of GAD, GAD3, that has been shown in certain fish species: *Coryphaenoides artmatus*, the deep sear armed grenadier, and *Carassius auratus*, the gold fish (Lariviere et al., 2002).

Martin and Rimvall (1993) first suggested that GAD65 is involved in GABA synthesis for vesicular release whereas GAD67 primarily functions in cytoplasmic GABA for metabolic purposes. Soghomonian and Martin (1998) extended this work and proposed that GAD65 synthesized most of the neuro-transmitter GABA under normal conditions. Based on the characteristic cellular localization, differing N-terminal domains, and interaction with co-factors, each isoform regulates the level of GABA. A differing role in the synthesis of GABA in the two isoforms have been observed in knock out mice studies. For example, the deletion of GAD65 gene does not significantly alter brain GABA levels in young mice (Asada et al., 1996). Contrastingly, GAD67 gene deletion resulted in mice born with low GABA contents that failed to survive due to cleft palate deficiency (Asada et al., 1997).

Studies from immunohistochemistry demonstrated considerable differences in the level of individual GAD isoform among cell types and regional brain distribution (Esclapez et al., 1993, 1994). Esclapez et al (1994) reported that the levels of GAD67 mRNA are greater than GAD65 mRNA in most brain regions. There is now reproducible evidence for a decreased expression of GAD67 mRNA in multiple brain regions such as the cortico-limbic regions of patients with schizophrenia, bipolar and major depressive disorders (Torrey et al., 2005).

4. The roles of GAD65 and GAD67 in neural development and its implication in autism

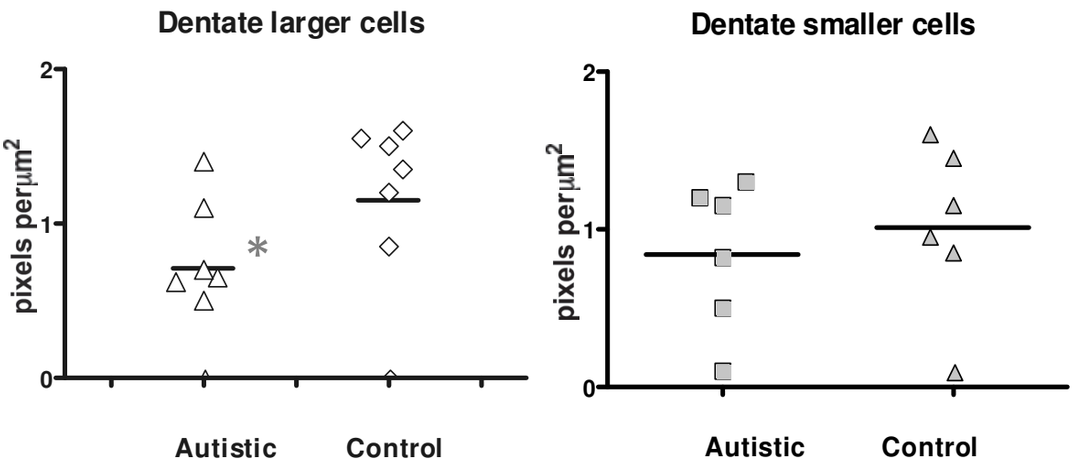
GABA is involved in the development and plasticity of the postnatal nervous system (McLean et al., 1996; Pisu et al., 2004). In the human cerebellum, both GAD65 and GAD67 mRNA are strongly expressed during development yet the two isoforms differ in their timing of expression. GAD65 and GAD67 mRNA are both present by gestational week 12 (Chan et al., 1997). For GAD67, the messenger level remains high and following a slight decrease maintains its abundance for the rest of the gestational period. In contrast, GAD65 mRNA levels decreases rapidly from GW12 and becomes undetectable by GW19 (Chan et al., 1997). Despite the apparent low activity of GAD65 in subsequent fetal development, GAD65 is important in maintaining GABA levels. While both GAD65 and GAD67 maintain GABA levels *in vivo*, GAD65 could act to powerfully offset perturbation to GABA synthesis in the event of a GAD67 deficiency. This was substantiated in an organotypic culture where the presence of GAD65 and GABA synthesis as well as the proliferation of GABAergic neurons was supported without GAD67. Interestingly, mutant mice lacking GAD67 had maintained their GABA contents. Additionally, there was a markedly increased number of GABA-containing neurites. In the absence of GAD67, the development of cerebellar Purkinje cells (PC) was sustained (Ji & Obata, 1999). In young mice, GAD65 may not be required (Asada et al., 1996) though it is indispensable in adult mice (Stork et al., 2000). GAD65 deficiency could lead to serious behavioral impairment as experimental adult rats who have reduced GABA content, to nearly 50% of normal values, in the hypothalamus and amygdala exhibited severe anxiety (Ji & Obata, 1999).

In humans, development of the visual cortex coincides with an increase in GAD65 expression. The additional GAD65 expression provides a larger pool of synaptic GAD for GABA release for the purpose of short term changes in neuronal activity (Feldblum et al., 1993; 1995) and further provides an agency for neuroplasticity. Electrophysiologically, GAD65 provides tonic inhibition and the short term effect balances more rapid fluctuation in excitation during development (Walls et al., 2010) and confers the balance between excitation and inhibition in development.

The failure of an adaptive control of GAD65 and GAD67, especially in circuits modulating emotions, may be related to defective emotional coping in times of stress. Dysregulated GAD67 have been linked to psychosis (Kalkman & Loetscher, 2003). One interesting note is that there appears to be a parallel between psychosis and autism. This is especially true in relation to aggressive behaviors such as temper tantrums, property damage, self injurious behavior, and so on. Some individuals with autism have an increase risk of hyperactive responses to emotional distress with a predisposition to acting out aggressively towards oneself and others. However, in these autistic individuals- who exhibit aggression- the relationship between emotional distress and the actual mechanism of autism is less clear. Certainly, an inherent abnormality of the GABA system could dampen the nervous systems' ability to shut off stimuli once it has been turned on. When GABA malfunctions start at the GAD65 loci where its developmental trajectory may have been perturbed during fetal development, it could likely lead to a long standing state of reduced GABAergic inhibition and increased neuronal hyperexcitability of stimuli.

Current autism neuropathology literature shows that there is a decreased level of GAD65 and GAD67 proteins in the cerebellum (Fatemi et al., 2002). Our study revealed that there is a also a decrease (51%) in transcript level for GAD65 (GAD65 mRNA) in a select population

of neurons neurons located in the dentate nuclei (i.e. the larger dentate neurons) -which projected into the thalamo-cortical circuit- compared to no change in the smaller dentate neurons- which are likely interneurons- in adult autism cases (Yip et al., 2009; figure 2 and 3). A deficiency of GAD65 in the larger dentate neuron population in the absence of a compensatory increase in neighboring GABAergic neuronal populations suggests serious deficiency in the ability of GAD65 to maintain GABA levels. To compound the GAD65 mRNA deficiency, there was a 40% reduction of GAD67 mRNA levels in PC that formed reciprocal connections to the dentate nuclei, inferior olivary complex, and the dentato-thalamic-cortical pathways; the PC is ultimately responsible for timing and gating of incoming hyperpolarizing impulse (Yip et al., 2007; figure 4). A decrease of GAD67 mRNA level in the PC of the cerebellar cortex in our subjects examined is consistent with a deficiency in the protein level of GAD67 in whole cerebellar homogenates (Fatemi et al., 2002) suggesting a direct relationship between protein and transcript level. Overall, this suggests that there is a lowered level of GAD67 in autism which can compromise the ability of neurons to maintain baseline GABA levels.



p=0.03, students t test

Fig. 2. Comparison of the level of GAD65 mRNA level in the dentate nuclei in the larger versus the smaller cells. There was a statistically significant difference reduction in the level of GAD65 mRNA (*p*=0.03; student's t test) between the larger dentate cells compared to the smaller cells in the autistic population.

5. Mechanism of neuroplasticity in the cerebellum in subjects with autism

Neuroplasticity balances deficiency of GABA through the modulation of the two isoforms. For example: GAD67 in contrast to GAD65, is strongly experience driven. The activity of GAD coincides with regulation of protein and mRNA levels during intense neuronal activity: stress stimulation (Uchida et al., 2011), seizure events (Walls et al., 2010), and chronic psychotropic drug treatment (Fatemi et al., 2009). GAD67 balances the cast of inhibitory plasticity in a dynamic manner as the developing organism acquired neuronal inputs from the environment. GAD67 is important for long term regulation of phasic neuronal activity, while GAD65 is recruited during tonic activity and as needed (Walls et al., 2010).

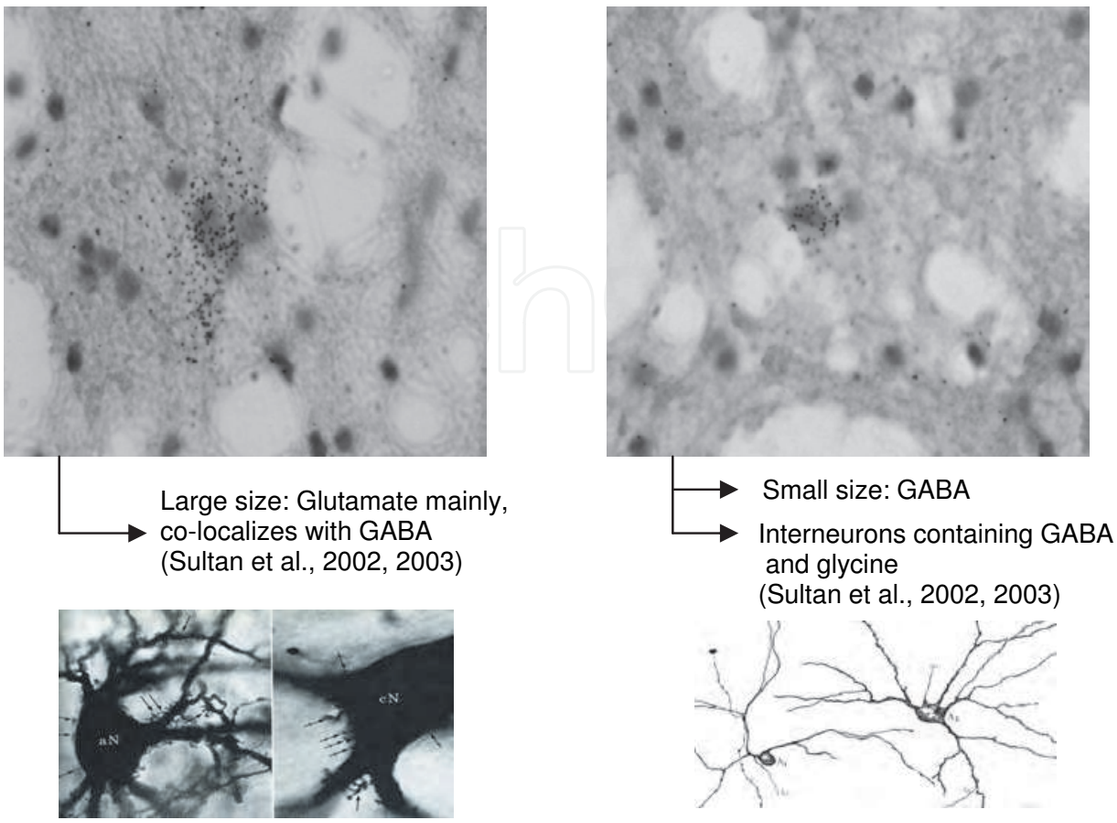


Fig. 3. The differential sizes of the dentate nuclei co-localize with different neurotransmitters. The larger-size dentate nuclei contains mainly GABA whereas the smaller-size dentate nuclei are GABAergic mainly as well as colocalizes GABA with Glycine in the interneuron population.

The inter-neurons in the molecular layer are agents responsive in plasticity mechanisms to balance GAD deficiency. Indeed, in the event of a GAD67mRNA decrease in PC, the authors observed a compensatory increase in basket cells in the cerebellar cortex of autistic individuals (Yip et al., 2008; figure 5). Inhibitory interneurons in the cerebellar cortex consist of basket and stellate cells (figure 6). The inhibitory nature of basket cells and stellate cells was clarified in the 1960s (Eccles et al., 1966) when antibodies became available for GAD. Each class of inhibitory interneuron contained GAD, and the synaptogenesis of these GABAergic neurons marks the differentation of basket and stellate cells (Simat et al., 2007).

6. The cerebellar circuitry in autism and conditioned learning: implications for behavioral treatment

Based on the study of GABA regulation described in previous sections, the authors propose a summary of a putative mechanism of "behavior in autism"- linking what is well known about the cerebellar circuitry to current understanding of behavioral output as being governed by a system of memory called long term potentiation (LTP) and long term depression (LTD) of memory. Afterall, it is the memory system that determines the behavior of an individual because each behavior is generated as a response to a pool of learned responses whether conditioned or not.

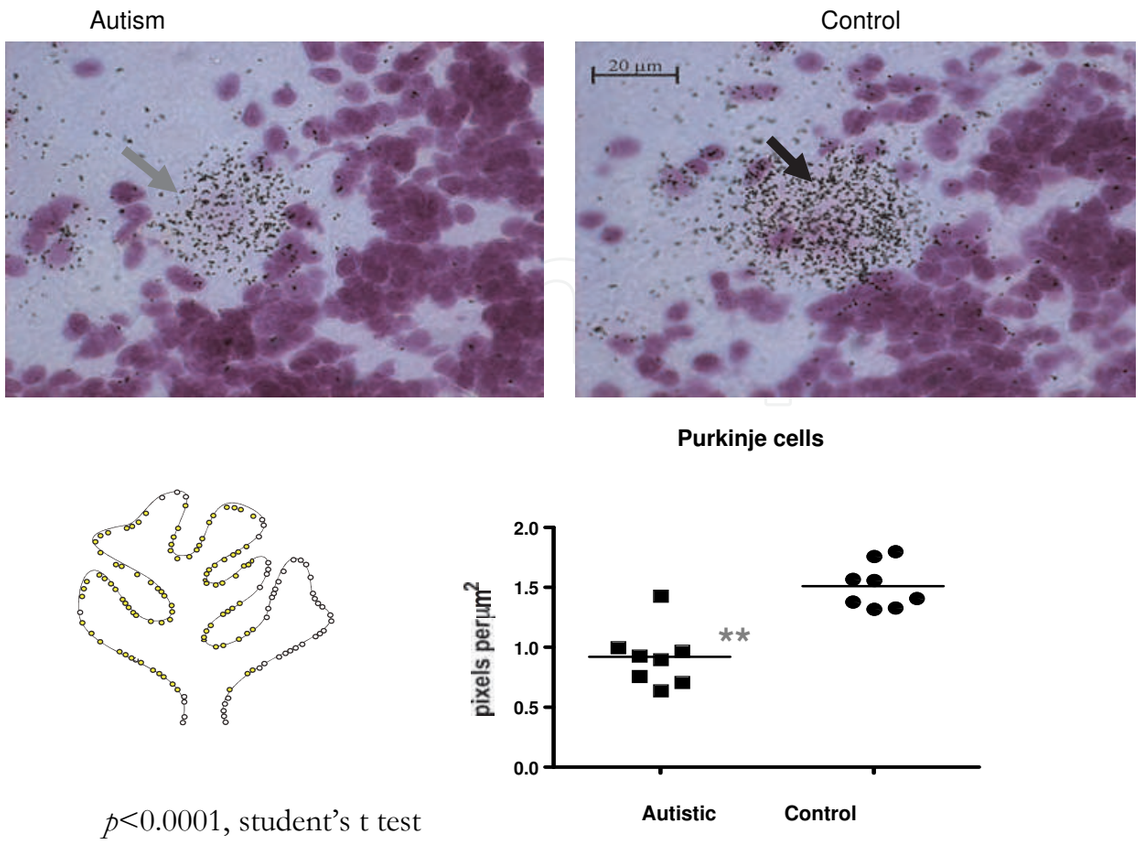
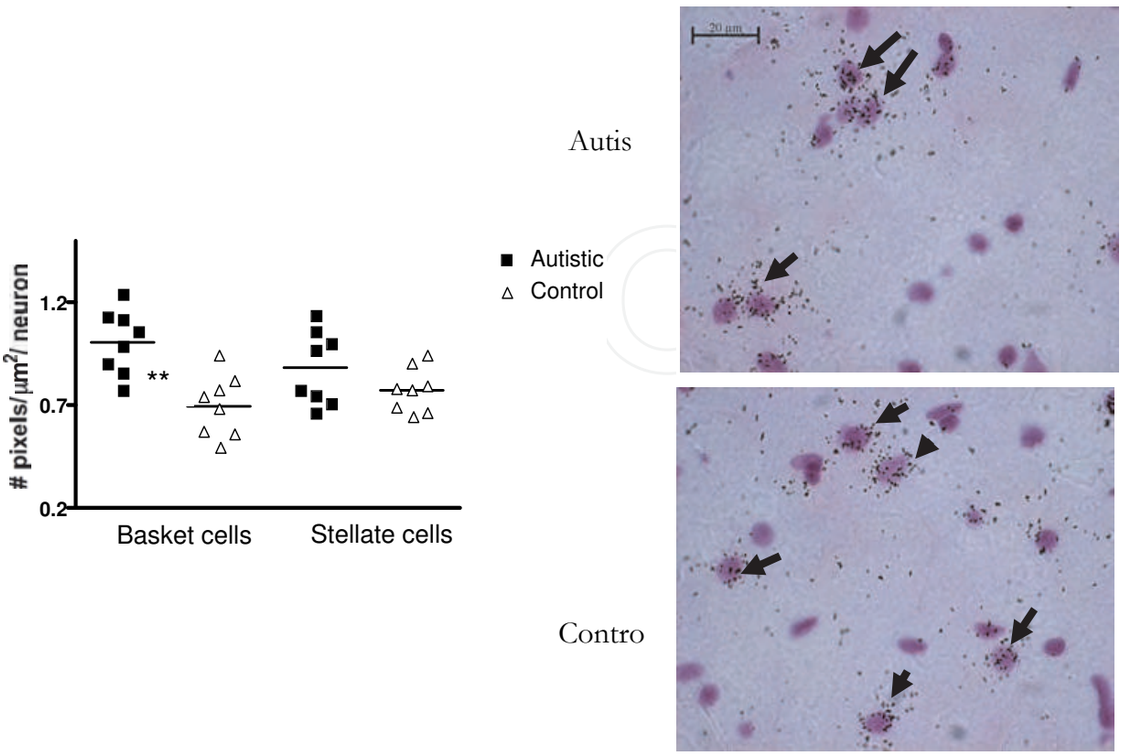


Fig. 4. Reduction in the level of GAD67 mRNA in Purkinje cells (PC) in the autistic compared to control (t(degrees of freedom)= …, p<0.0001). Note the sparseness of speckled labeling of GAD67 mRNA-positive PC soma in the autism compared to the control case.

The cerebellum has a role pertaining to complex behaviors such as cognition and emotional processing that include planning and impulse control (Schmahmann, 2010; Stoodley, 2011) and is more than a motor and sensory processing device as previously believed to be. Its simple, modular structure holds the greatest promise for uncovering the "holy grail" as it relates to the neurological system. With less uncertainties, cerebellar circuitry offers a more viable model to derive an understanding of how (almost directly from molecules and cells) synapses and circuits could influence one's behavior (i.e., learning and memory) as compared to the immense complexity of the neuronal configuration within the cerebral cortex. One of the pioneers who elaborated on the idea of cerebellar neuronal structure and its circuit connections as it related to motor learning recently expressed strong support for a plausible, if not important, role of cerebellar circuitry in the dysfunction within information processing (Ito, 2008). Specifically, perturbation of GAD in the cerebellum of our subjects with autism is presented in relation to the circuit connection according to Ito in figure 7.
The cerebellum consists of a well defined structure containing a unique, compartmental, modular structure with complex signal transduction processes in distinct cerebellar neurons. The study of neuronal circuits has attracted a great deal of interest in understanding how these specific entities operate to generate one's mental activities and will continue to be the forefront of modern neuroscience. Factors that allow for this included an unusually well



(Simat et al., 2007).

Fig. 5. Increased level of GAD67 mRNA in the basket cell interneurons of the cerebellar cortex in the autistic versus the control group as evidence of neuroplasticity mechanism (-p<0.0001). Speckled labeling represents GAD67-mRNA-positive cells.

defined circuit diagram. The cerebellar circuitry is essentially composed of a relay station in the deep cerebellar nucleus (DCN) and a cortical 'side loop'. Cerebellar output to pre-motor centers originate in the DCN which in turn are driven by direct excitatory input from the mossy fibers (MFs). Additionally, it is modulated by the inhibitory input from PC axons, which conveys computations and interactions in the PC. These computations will be performed upon a matrix of subtle and informationally rich excitatory Parallel fiber(PF) input (~200,000 axons), massive and synchronous excitation produced by the one climbing fiber (CF) axon innervating each mature PC, an input from inhibitory inter-neurons. This unusual anatomical configuration inspired a model of motor learning proposed that the PF-PC synapses could provide contextual information. Additionally, the CF-PC synapses could signal an error in motor performance that required alterations of subsequent behavior, and that the conjunction of these two signals could strengthen the PF-PC synapse to create a memory trace for motor learning (Ito, 2002). Compared to other brain areas, the cerebellum has the most organized cellular arrangement consisting of PCs, basket cells, stellate cells, granule cells, and interneurons along with mossy, parallel and climbing fibers. The precision of the cerebellar circuitry has inspired numerous proposals to emulate the cerebellum as a universal learning machine (Ito, 2006, Welsh et al., 2001, Raymond et.al., 1996).
The emerging view of cerebellar circuitry pushes strongly in the direction of regarding this structure as a real-time processing device, whose output is governed strictly by the pattern of inputs received from the other nervous system areas for sensory, motor, or cognitive task

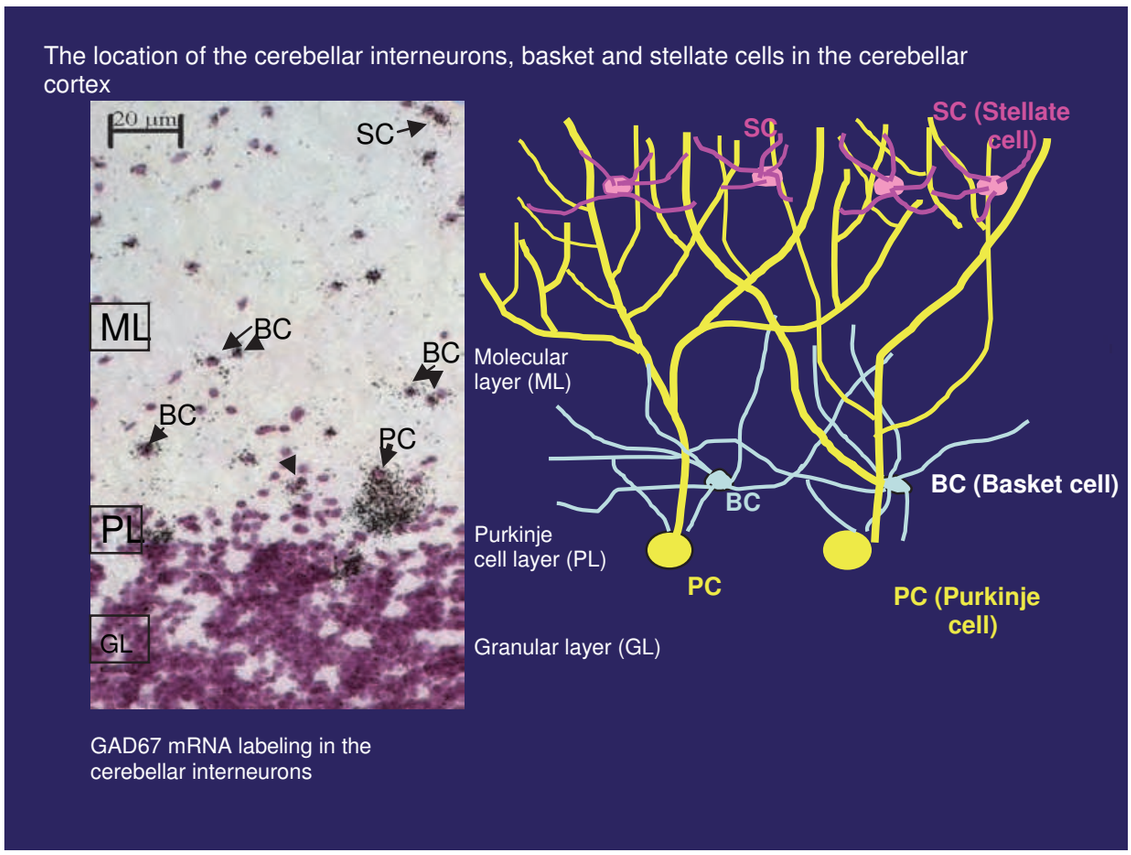


Fig. 6. **The relative location of interneurons in the cerebellar cortex.** Basket cells are located at the PC layer (PCL) whereas stellate cells (SC) are locate at the PC dendritic tree. Speckled labelling represent GAD67 mRNA-positive cells.

completion (Bower, 2002). The following diagram attempts to summarize current literature views of the cerebellar circuitry in LTP and LTD. The general consensus of those in the field of LTP learning in the cerebellum is that it operates precisely upon moment-by-moment task demand that can be conditioned. Recently, using an eye-blink conditioning mode, stimulation of the mossy fibers in the cerebellum elicited a potentiation of memory, although short lasting, at the granule cell-to-PC synapse indicating and that plasticity can be induced through training in animals (D'Angelo et al., 2005; Ohyama et al., 2010). The literature supporting plasticity changes in the brain, in particular the cerebellum, in response to conditioning is extensive (Aiba et al., 1994; Coesmans et al., 2004; Weber et al., 2003; Wadiche & Jahr, 2005) This type of plasticity conditioning has been observed mainly in animals, and may have correlates in human learning since both the substrate and the structure of the brain are the same. It may be for this reason that ABA-based treatments proved to be successful in improving the behavior of individuals with autism (Glen et al., 2005 in the Wisconsin Early Project). In this project, 24 children with autism were trained according to an early intensive behavioral treatment developed by at the University of California-Los Angeles (UCLA) and the outcomes after 4 years of treatment were that 48% of all children showed rapid learning including cognitive, language, adaptive, social, and by age 7, were succeeding in regular education classrooms. It is tempting to speculate whether

training could have the effect of modifying brain circuitry and adjusting the deficient transcriptional machinery. Answering a question like this would provide substantiation to clinical professionals working with individuals so that redirection of behavior is congruent with the underlying brain (dys)function and the molecular mechanisms of the disorder, as shown in figure 1. Also, it will be an initial step into a much needed interdisciplinary collaboration between biomedical and applied behavioral research.

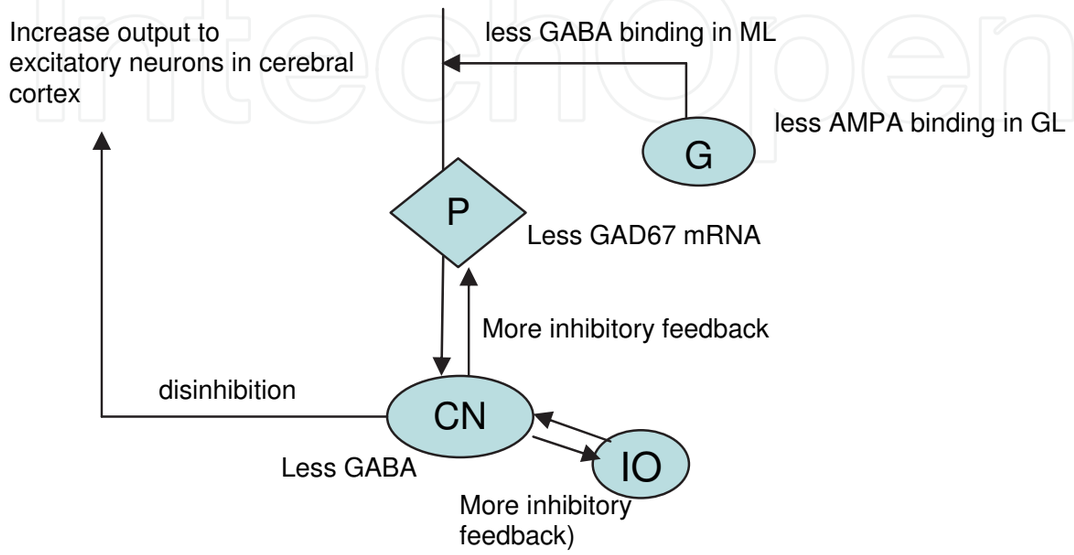


Fig. 7. A diagrammatic summary of the findings on the GABAergic system in the autistic cerebellar cortex from the laboratory of Dr Gene Blatt, Boston University, in which the neurobiological work discussed was performed (some of the results not presented in this chapter). Overall, our results showed that there is a down-regulation in inhibitory GABAergic input to Purkinje cells (PCs) and a down-regulation to the dentate nuclei (CN). The resulting cascading event lies in the circuitry connection such that an overall disinhibition occurs in the cerebellar circuitry from the feedback circuit of the PC-CN and the CN to the inferior olive (IO). Ultimately, lowered inhibition will result in increased output to excitatory neurons in the cerebral cortex, which the dentate nuclei project to, since the balance between inhibition and excitation is perturbed. A background inhibitory synaptic drive in addition to the excitation is necessary to maintain normal PC output. Therefore, an altered balance of inhibition in the PCs is likely to adversely affect glutamate receptor functions essential for the normal maintenance of LTP/LTD.

7. Future studies - how to connect brain function to the child's performance in the natural environment

The sum total of neuronal output is the balance between excitatory and inhibitory neurotransmitter signals. A reduction of inhibitory GABA signals predicts an overall perturbation of neuronal signals that favors a more "excited output which is reflected in numerous parameters of brainwave signals in autism that can be observed from infancy (Ahmadlou et al., 2010; Bosl et al., 2011). An illustration of a simple EEG tracing obtained in a preliminary study is shown in figure 9 (collaboration with Dr. Sara Davis). Briefly, the

brain waves of a typical child versus an autistic child were measured using EEG during the following conditions: mathematical processing task, reading task, block building task, and at rest. Preliminary results reveal that there is a significant difference between a typical child and an autistic child during these four monitored conditions. It is interesting to note that the autistic child exhibited a tendency towards "normalization" when building the blocks as compared to the other three conditions.

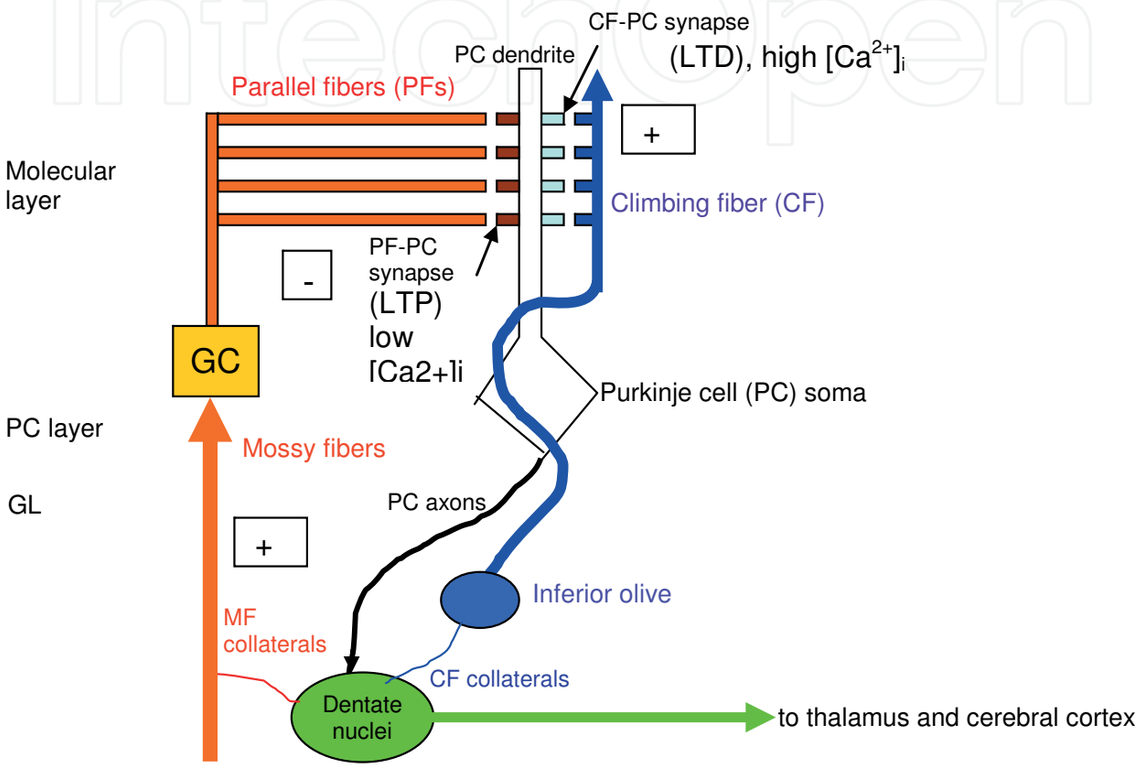
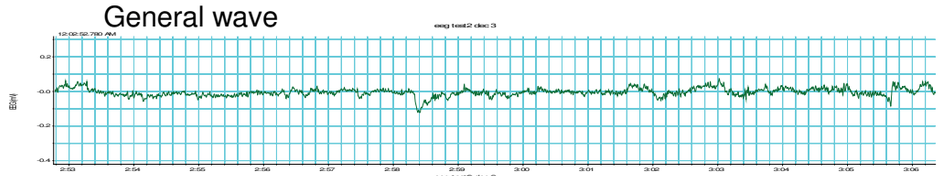


Fig. 8. The converging synaptic site of CF-PC and PF-PC on PC dendrites in the molecular layer is the location for the mediation of LTD or LTP. The components of the cerebellar circuitry belong to a larger neuronal output that is responsible for LTD by amplifying somatic responses through increasing the activity of the voltage-gated [Ca^{2+}] channels or decreasing responses through lowering the influx of [Ca^{2+}] into PCs. Therefore, an imbalance will occur if the ratio between LTD/LTP changes in the molecular layer. Since the granular layer (GL) is also involved in LTP in an activity-dependent manner, the granular layer LTP that is mediated through NMDA receptor activation will increase as a neuroplasticity mechanism. Abbreviations: CF, Climbing fibers; PC, Purkinje Cell; PF, Parallel fiber; LTP, long term potentiation of memory; LTD, long term depression of memory, GL, Granular layer; GC, Granule Cell

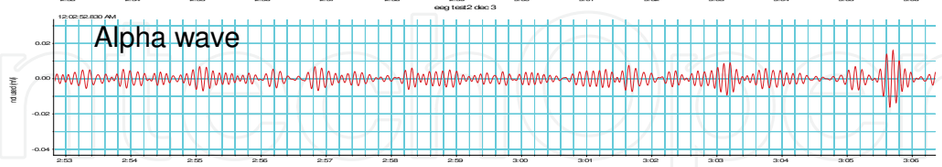
To date, many advances have been made in developing an electrophysiological recording device that is portable, reasonably accurate for documenting brainwaves, and has the ability to estimate neural activity from various brain regions. The quantitative electroencephalograph (qEEG) holds such as a promise. QEEG assessment allows to identify anomalies in brain function. QEEG maps (such as the ones shown in Figure 10 are typically constructed using

Typical **Brain wave when relaxed and eye open**

General wave

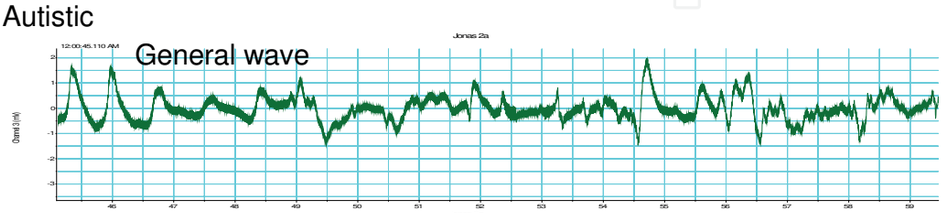


Alpha wave

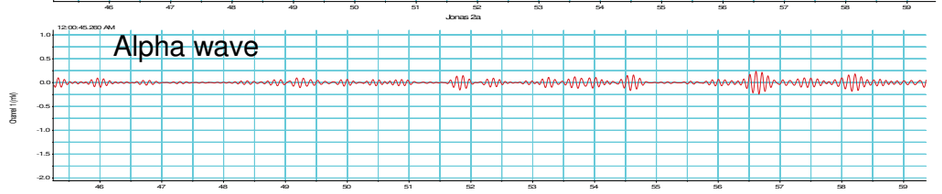


Autistic

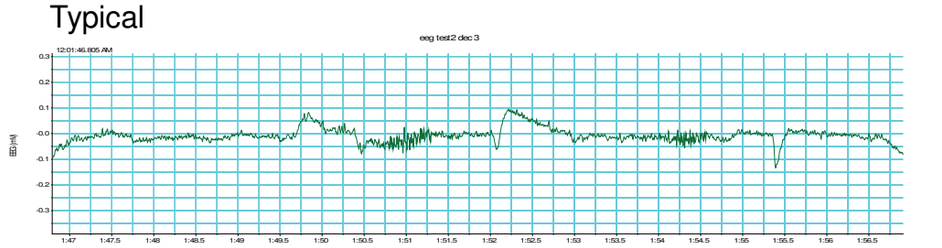
General wave



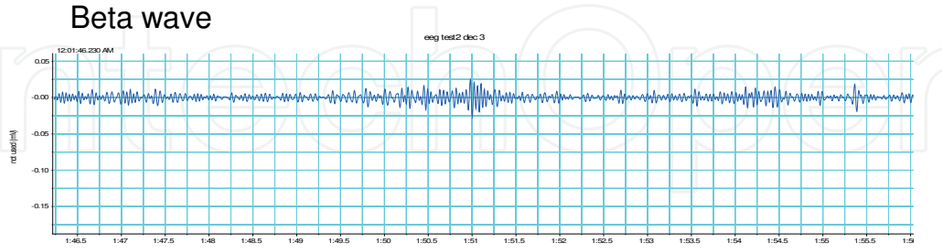
Alpha wave



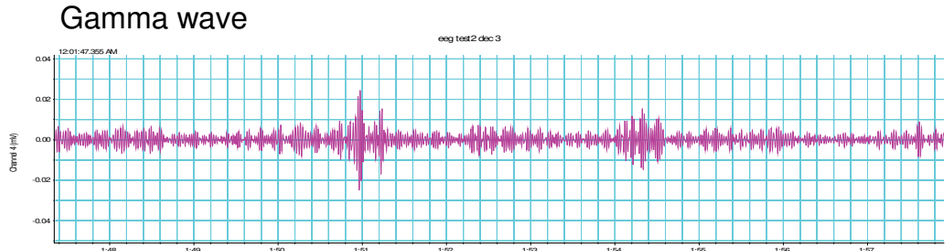
Typical



Beta wave

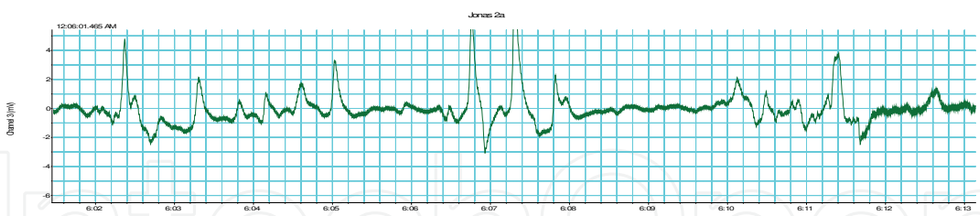


Gamma wave

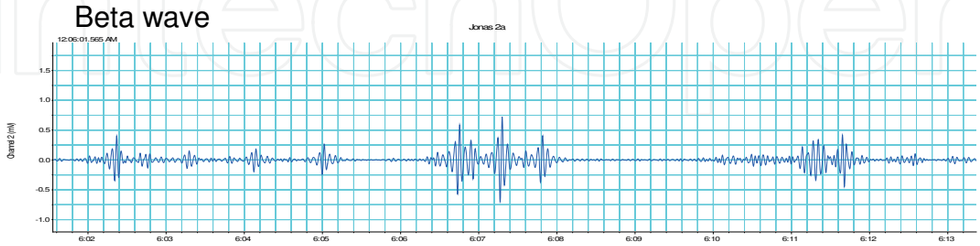


Mathematical Processing

Autistic



Beta wave



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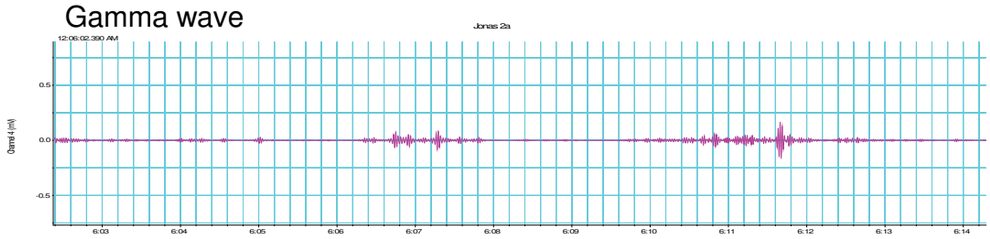
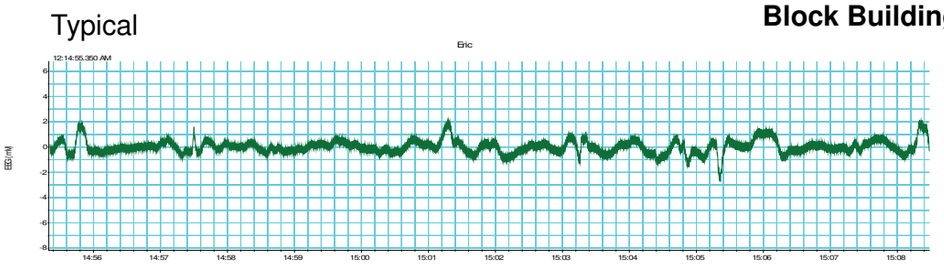


Block Building

Typical



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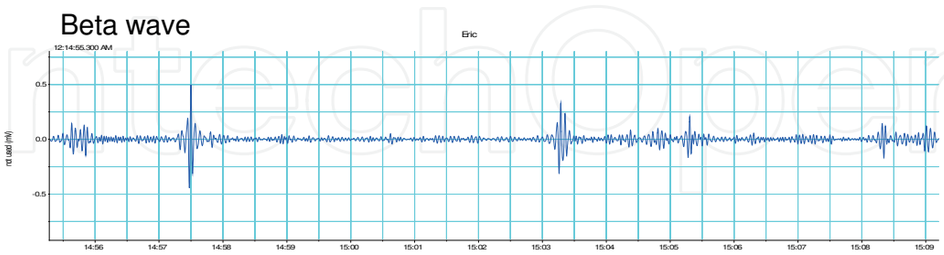

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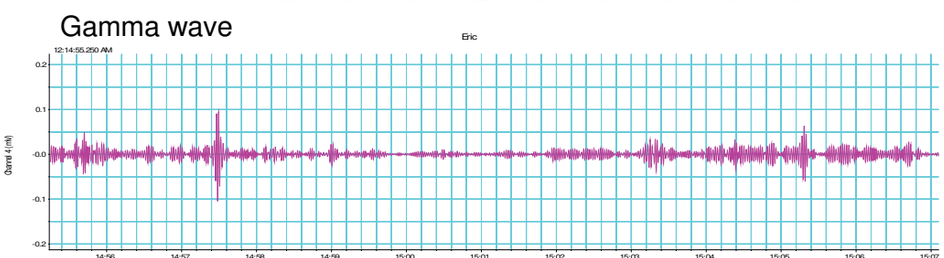

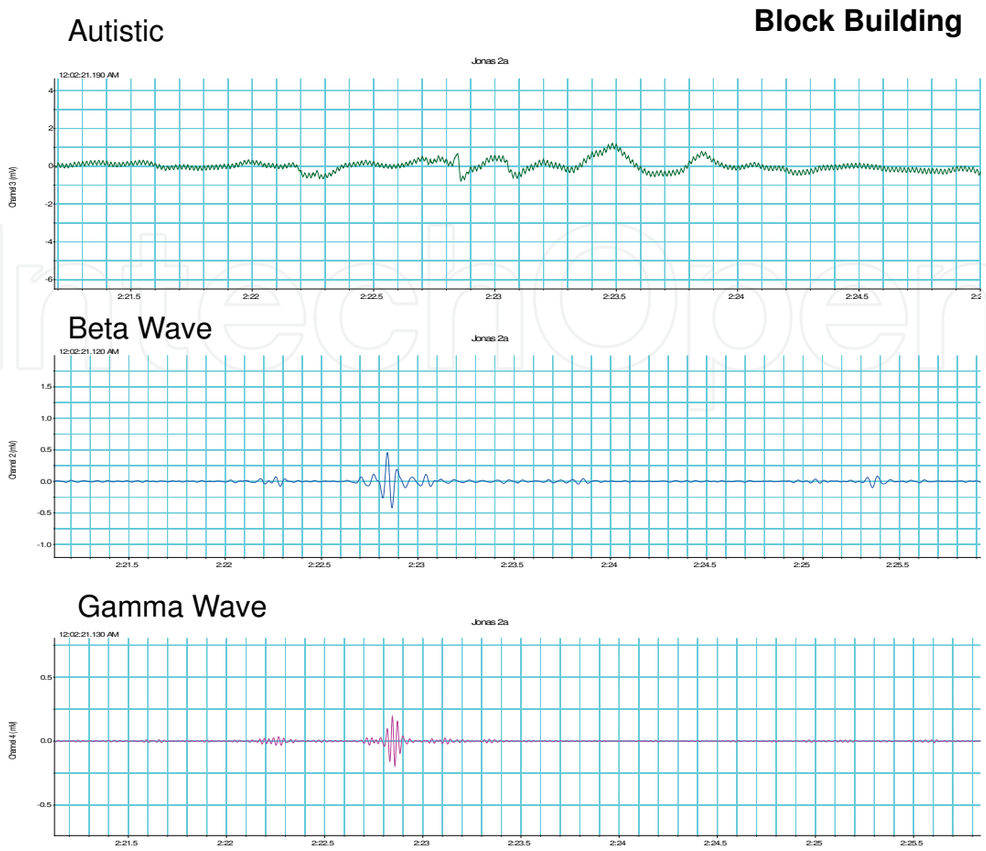

Fig. 9. The brain waves of a typical child versus an autistic child were measured using EEG at rest and while performing three tasks: mathematical processing, reading, and block building. Preliminary results reveal that there is a significant difference between a typical child and an autistic child during these tasks. It is interesting to note that the autistic child studied exhibited a tendency towards "normalization" in general of brain waves when building blocks as compared to the other tasks.

19 electrodes based on the International 10-20 system (Jasper, 1958). These maps are quantitative summaries of EEG characteristics such as frequency, amplitude and coherence emmitted during different conditions or tasks. Software programs along with the qEEG devices that are United States Food and Drug Administration (FDA) approved can then be used to calculate various indices of brain function such as connectivity, amplitude, phase lag, and brain performance index (Thatcher et al., 2005). One advantage of this method is that it can be widely applied, is less costly as Magnetic Resonance Imaging (MRI), and less invasive than Positron Emission Tomography (PET). Thus far, the qEEG analyses in autistic individuals showed aberrant activity in the frontal lobe (Pop-Jordanova et al., 2010).
The authors have collected qEEG brain maps for both an autistic and a control subject during resting states using the same system as Pop-Jordanova et al (2010)(i.e., BrainMaster amplifier and NeuroGuide software) . Although slight individual differences are typical in qEEG measurement these maps illustrate the more fundamental disparities of brain activity in autistic individuals (Figure 10). Our aim for future studies is to connect neurological deficits to treatment regimens Further investigations will look at the effects of language and

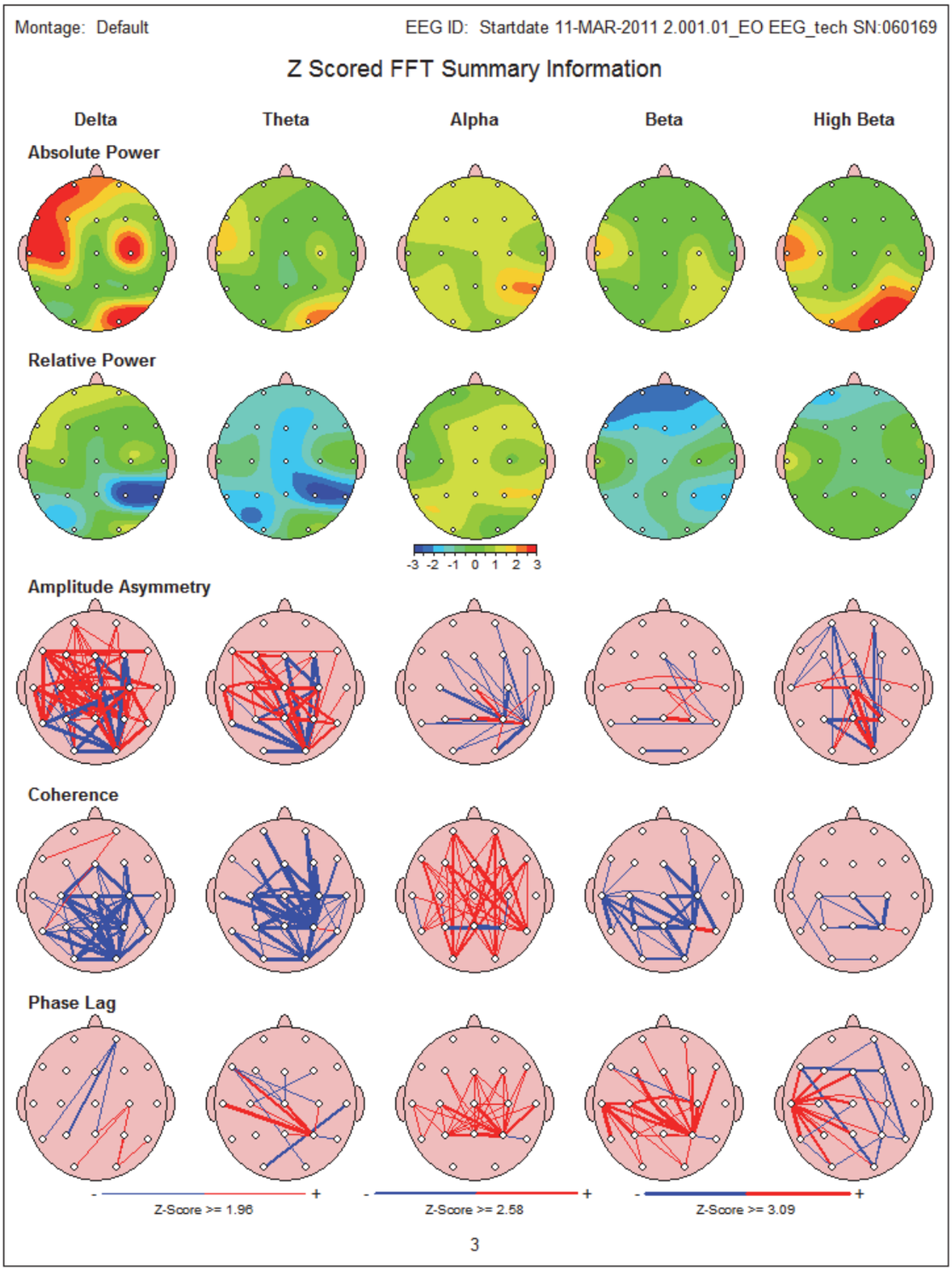

Fig. 10A. A brain map using qEEG obtained from Brainmaster and NeuroGuide of a volunteer with autism (A) and a control (B) during eye open relaxed state.

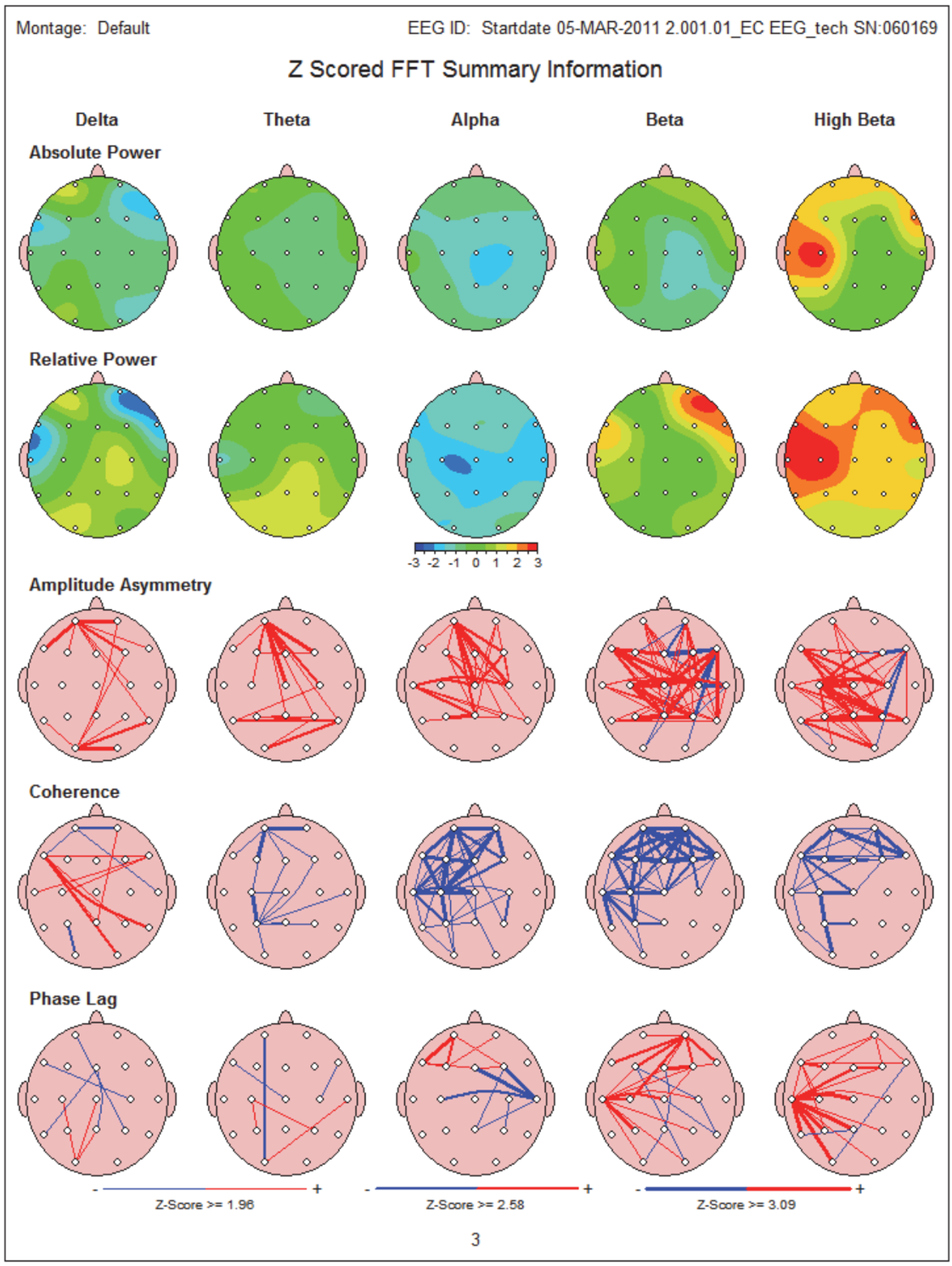

Fig. 10B. A brain map using qEEG obtained from Brainmaster and NeuroGuide of a volunteer with autism (A) and a control (B) during eye open relaxed state.

social communication treatments on brain connectivity, combining behavioral assessment with electrophysiological measurement. Such an approach has been implemented successfully in evaluations of neurofeedback training (Pineda et al., 2008) and acupuncture treatments (Chan, 2009) with subjects mostly diagnosed as high-functioning autism. Our goal is to extend these initial efforts to a wider range of autism spectrum disorders and treatments, particularly focusing on the domains of verbal and non-verbal language and social-communication in those diagnosed with moderate to severe autism.

A widely implemented ABA-based treatment to target communication skills innon-verbal, severely autistic children is the Picture Exchange Communication System (PECS). PECS follows a manualized treatment protocol for prelinguistic communicators that involves six phases: In *Phase I: Physical Exchange*, children are instructed to exchange a graphic symbol for a desired item (often a snack item or toy). In *Phase II: Expanding Spontaneity*, children learn to exchange a symbol with a communication partner who is not in the immediate surrounding. In *Phase III: Picture Discrimination* the child is taught to discriminate among symbols for requesting. Subsequently, in *Phase IV: Sentence Structure*, the child learns to put an "I want" symbol onto a blank sentence strip, along with the symbol for a desired item, and to exchange the sentence strip with a partner. In *Phase V*: *Responding to "What do you want,"* the child is trained to respond to a direct question. Finally, *Phase VI*: *Responsive and Spontaneous Commenting* uses previously acquired skills to elicit a response to additional questions (i.e., "What do you see?") and encourage spontaneous commenting (Bondy & Frost, 1994)

An autistic child's ability to recognize pictures is relatively intact due to preserved visuo-spatial skills (Mirenda & Brown, 2009). It is expected that successful intervention will be reflected in enhanced brain connectivity and overall gain in cognitive capacity. Additionally, it is expected that individuals who are slower to learn- and/ are unable to proceed to later PECS phases -have brain connectivity patterns that are different from their more successful counterparts, and hence could reveal both a brain and performance marker in the more challenged subtypes. QEEG data will be critical in measuring treatment effects at the neurophysiological level, individualizing treatments for participants and making refinements to the treatment protocol as necessary.

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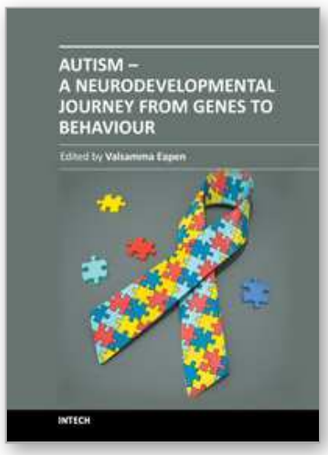

Autism - A Neurodevelopmental Journey from Genes to Behaviour
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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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