Chapter

INA Early Intervention for Babies at Risk

Hagit Friedman, Marina Soloveichick, Amir Kushnir, Chava Kasher, Caroline Barmatz and Omer Bar-Yosef

Abstract

Brain and nervous system development are experience dependent. Indeed, the sequence of development is laid out genetically, but early environmental events are major contributors to the system's development and optimal functioning. Various fetal injuries and birth trauma make babies vulnerable to developmental problems: cerebral palsy, seizures, abnormal muscle tone, delayed developmental milestones, sensory integration, and more. Our goal in the study presented here was to improve the neurodevelopmental track of babies at risk using Infant Neural Aquatic. Parent and baby dyads who met initial criteria were recruited for a 5–6 months intervention period through an open invitation, followed by a conversation and signing informed consent. In the beginning and end of intervention period, participants completed questionnaires, and developmental features of the babies were assessed using analysis of neuro-motor and vocal characteristics. Significant neurodevelopmental delta between values at the end and beginning of intervention period, comparing intervention and control, is described, and the strength of INA specific intervention tool is analyzed.

Keywords: brain development, brain injury, early neurodevelopment, early intervention, developmental time windows, developmental insult, premature babies

1. Introduction

1.1 Early intervention

In the old Talmud, an imbecile, deaf-mute, and a minor were included in the same category related to religious obligations (Baba Kama 55 page B). This approach was explained as probably the earliest expression of the significance and power of early intervention—for babies and for disabled people.

In recent decades, we return to this approach and look for suitable and efficient early intervention models in order to successfully cope with developmental insults.

Training with babies in an aquatic setting has been found to benefit and promote infant health and development [1–3], being based on the physical properties of water and their physiological outcomes on the neuromotor [4–6], cardiovascular [7, 8], and respiratory functions [3]. Specifically, training with babies in an aquatic setting adapted for young babies with developmental risk may strengthen the function of autonomic parasympathetic nervous system and improve the

development of neural circuits through better brain perfusion and sensory-motor training [1, 2, 9, 10].

In warm water, increased environmental pressure advances deep lung ventilation and higher lymphatic and venous return from the periphery; higher levels of blood and lymph entering the heart's right atrium cause slight bradycardia, producing a calming effect; most important for these infants, the water buoyant force causes the proprioceptors to cease registration of gravity; and an automatic reduction of muscle tone ensues. The benefits of reduced muscle tone linger for some hours following immersion. In these beneficial conditions, training is most effective both for sensory, emotional, and neuromotor purposes, and active parent role in this process is an additional advantage.

Training with young babies at risk, in an aquatic setting, may not cure severe brain lesions such as cerebral palsy; however, implying specific training approaches in specific developmental time windows may allow early effective intervention [11–15] which may eventually improve brain development.

This was our basic concept when we started our journey into the project, yet our findings showed us that our training protocol may have a deep neuro-power, more than we could foresee.

1.2 Early brain development and brain lesions

Neurodevelopmental syndromes are a continuously growing issue. These are impairments in the growth and development of the brain and CNS which appear in a variety of emotional, cognitive, motor, and social skills. One most important question when diagnosing and treating young children concerns the critical developmental time window through which chances for improvement would be strongest. Considering the fragility of young babies who are at developmental risk and the general tendency to postpone definite developmental diagnosis, the consideration of intervention should include neurological background of developmental mile stones.

During fetal development, a temporary assembly progresses in the subcortical future white matter, situated between the intermediate zone and the developing cortical plate, named cortical subplate [16]. As widely described in our recent paper [17], the subplate is thickest around the time of high production of oligodendrocyte father cells (29 weeks PMA), and is absorbed gradually until around 4 months postterm, with relocation of fiber terminals into the cortex [18, 19]. Most of its networks run through the (future) periventricular white matter. The size and duration of the subplate visibility correspond with cortical fiber complexity, being considered a recent phylogenetic structure that enables the increasing complexity of cortical circuitry [20].

The cortical subplate is a transmission complex for the neural projections of the developing cortical circuits and a regulating component that orchestrates neural network activity [21, 22]. Hence, subplate neurons are important for precise wiring and functionality of the cerebral cortex—they make initial temporary synapses between thalamic axons and their destinations in the early C4 layer [23].

SCP neurons, with their numerous synaptic contacts, are important factors that influence cortical development and ripening [24–26]. In the time gap of their presence, the SCP neural circuits are prone to hypoxic insult [27], which may cause long-term influence on brain development and functional deficits in various aspects. The time window of SCP circuits' high action is also the time window when young infants born premature make their first surviving out of utero.

1.3 Neurodevelopmental impairments

Neurodevelopmental impairments range from MND (minimal brain deficit) to ASD (autism spectrum disorder) and CP (cerebral palsy) [28–34]. Despite recent

technological and scientific advance, there is currently no cure for severe neurodevelopmental impairments. However, various therapies may reduce the traumatic effect of brain lesions when diagnosed and treated during specific time windows in early infancy. Hence, the first weeks of baby's life may be critical for brain development through early and effective intervention.

The babies participating in our study were born premature and participated in this research during cortical subplate activity time window. Average birth percentage of preterm babies is around 10% and it is continuously rising. Prematurity is the global second frequent cause of death among babies. Although new medical tools enable more premature babies to live, many are at high risk for brain damage [29, 33, 35, 36] and neurodevelopmental insults [30, 34].

For example, cerebral palsy in premature neonates is caused mainly by developmental brain injury at the white matter of the brain—periventricular leucomalacia (PVL), due to bleeding in the brain (IVH, ICH), oxygen or blood deprivation (hypoxia, anoxia) in the brain [29, 32, 33]. Periventricular leucomalacia may cause severe, long-term damage to brain tissue [37–40]. Common symptoms of CP include lack of muscle coordination while performing voluntary movements (ataxia), and stiff or tight muscles and exaggerated reflexes (spasticity) with associated cognitive impairments.

Autism spectrum disorder (ASD) is the joint name for neurodevelopmental impairments characterized by abnormal social interaction, communication, limited range of activities and areas of interest [41], and typical motor impairments [42–53]. Being considered as sharing a similar mechanistic basis [54], previous ASD subcategories were unified under DSM5 (2013), and the classification today is based on severity of symptoms and level of disability.

There is a remarkable increase in the number of children diagnosed with ASD over the past 30 years, from less than 0.1% [55, 56] to ~1% [57] and more. Among infants at risk, premature infants have a five times higher risk of developing ASD, and a significantly high incidence of autistic symptoms was identified in premature infants [58, 59]. Changes in diagnostic criteria, different assessment tools, and increased public awareness may be only partially responsible for the increase in ASD epidemiology [60]. Studies indicate that genetic, neurological [59, 61–66], and environmental [67–72] factors are involved in the emergence of autism spectrum disorder (ASD).

Prenatal exposure to particulate matter solid fuels and traffic-related air pollutants, especially in the third trimester of prenatal development [67], link the ambient epigenetic aspects with internal genetic vulnerability due to lower, enzymatically based, removal ability of harmful remnants from infant's body. Indeed, these findings are in agreement with recent neurological understanding about the developmental time window of subcortical plate (SCP) during late prenatal and early postnatal period.

Early and effective intervention, through the important developmental time window of cortical subplate activity, may minimize neurological and functional deficits.

2. Basics of INA intervention approach

We have developed a unique training model for water—INA (Infant Neural Aquatics). The model consists of repetitive bilateral motor training and sustained moderate aerobic activity and their influence on desensitization and reprocessing of adverse events in utero and after birth.

After parents signed informed consent, INA was conducted in the hydrotherapy pool— babies were placed in warm water in vertical and horizontal positions,

supported by the buoyancy of water and the caring hands of parent or therapist. Training started with a set of pre-structured movements through which parents practice handling of the infant in the water, in a way that enables free and integrated movement, eye contact, vocal communication, and increased confidence.

Figure 1.
INA (Infant Neural Aquatics) approach at work: Encouraging eye contact.

Figure 2.
INA (Infant Neural Aquatics) approach at work: Relaxed floating.

Figure 3.
INA (Infant Neural Aquatics) approach at work: 8 shape delicate mobilization.

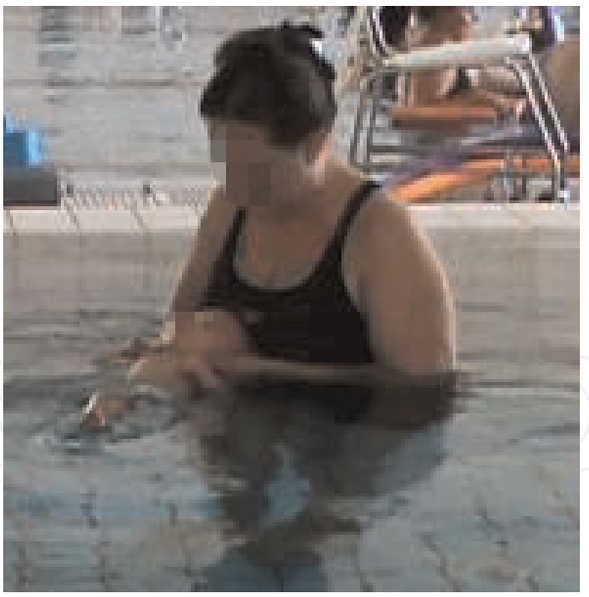


Figure 4.
INA (Infant Neural Aquatics) approach at work: Passive mobilizatio.

Working technique employed was modified for young and prematurely born Infants, including: passive mobilization, various rotations, relaxed floating, 8 shape delicate mobilization when the infant is supported under occiput and rib cage. Infants were video recorded during water sessions, under water and above water, once a week along 14 consecutive weeks (**Figures 1–4**).

3. Developmental track of babies

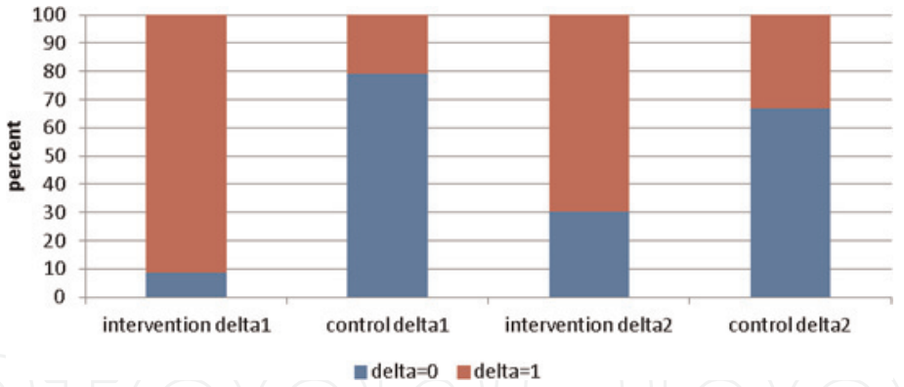
Developmental track of the babies with early intervention employing the INA approach was conducted at fixed time points using the non-intrusive General Movements (GM) tool [73–75]. The babies showed about 70% delta in developmental improvement comparing w/wo INA when the babies were around 55 wPMA.

Using the developmental tool ABAS (Adaptive Behavioral Assessment Scale) [76], the children showed about 40% delta in developmental improvement comparing w/wo INA, when the babies were around 1.5 years old (**Graphs 1, 2**).

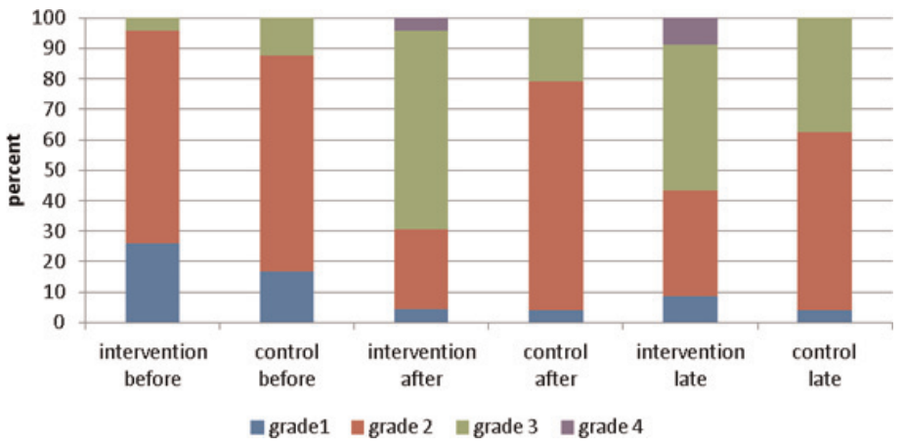
Intervention group. 78.27% of the subjects got the same results in delta1 and delta2 (for 8.70% both delta are equal 0 and for 69.57% both delta were equal 1), 21.74% of the subjects did not get the same results in delta1 and delta2—delta1 = 1 and delta2 = 0 (no opposite cases). We calculated the kappa coefficient (system consistency) = 0.3575 (confidence limit 95% is −0.0242 till 0.7393). We conducted McNemar's Test (significance of results), P = 0.0625.

Control group. 87.50% of the subjects got the same results in delta1 and delta2 (for 66.67% both delta were equal 0 and for 20.83% both delta are equal 1), 12.50% of the subjects did not get the same results in delta1 and delta2—delta1 = 0 and delta2 = 1 (no opposite cases). We calculated kappa coefficient (system consistency) = 0.6897 (confidence limit 95% is 0.3774 till 1.000). We conducted McNemar's Test (significance of results), P = 0.2500.

In order to test if group (w/wo early intervention) and the babies' preliminary grades were dependent, we used Fisher Exact test and got non-significant result (P = 0.5806), which proves no link between group (w/wo early intervention) and babies' developmental grade. In order to test if group (intervention/control) and the babies' grades at 55 wPMA were dependent, we used Fisher Exact test and got



Graph 1.
Difference in developmental tracks between before and after early intervention period (delta), in group with INA (blue) compared to group without INA (red), at the age of 55 wPMA (delta1) and at the age of 1.5 years (delta2).



Graph 2.
Developmental grades before, immediately after, and 1 year after early intervention period.

significant result (P = 0.0016), which proves a link between intervention and infant early developmental grade.

In order to test if group's grade (intervention/control) and delta1 were dependent, we used Fisher Exact test and got significant result (P < 0.0001). In the intervention group. 8.70% got delta = 0, and in the control group. 79.17% got delta = 0. In order to test if group's grade (intervention/control) and delta2 were dependent, we used Fisher Exact test and got significant result (P = 0.0199). In the intervention group. 30.43% of delta = 0, and in the control group. 66.67% got delta = 0.

4. Conclusions, applicative potential, and future aims

Our results show significant improvement in developmental tracks of babies receiving INA compared to babies who did not, that is, delta in developmental tracks, between before and after early intervention, is ~40% higher when babies receive INA as observed without INA.

Screening of our videos, recording INA practice with the babies, we interpret that in addition to the significant benefits of the water's physical environment (described above), INA model functions as a therapeutic tool for the babies who experienced a trauma, much like the modern variants of EMDR (Eye Movement Desensitization and Reprocessing) model [77]. The bilateral passive and active stimulation and movement during INA training cause a scheduled activation of both

right and left cortical hemispheres, unlock the traumatic experience in the right hemisphere, promote new connections in interhemispheric neural cycles, contributing to the high delta scores in the participants who received INA compared with those who did not.

We assume that longer intervention periods would keep the high delta scores to older age, allowing the brain more training and a longer period of enhanced conditions.

In the next stage of the project, we define the correlation between concentration curves of biomarkers related to brain injury in the participants' body fluids, and neuro-developmental track.

Indeed, the research described here directs the light on a certain vulnerable group of babies. However, the scientific and clinical products of this project, when properly tuned, may be successfully applied to various groups who are at developmental risk—children and youth diagnosed with post-trauma, or under extreme/acute emotional load, etc.

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References

[1] Vignochi C. Effect of aquatic physical therapy on pain and state of sleep and wakefulness among stable preterm newborns in neonatal intensive care units. Revista Brasileira de Fisioterapia. 2011;**14**(3):214-220

[2] Zelazo PR, Weiss MJ. Infant swimming behaviors: Cognitive control and the influence of experience. Journal of Cognition and Development. 2006; **7**(1):1-25

[3] Ahrendt L. The influence of infant swimming on the frequency of disease during the first year of life. In: Eriksson BE, Gullstrand L, editors. Proceedings of the XII FINA World Congress on Sports Medicine. Göteborg: Chalmers Reproservice; 1997. pp. 130-142

[4] Attermeier S. The use of water as a modality to treat an infant with mild neurological dysfunction. A case report. Physical & Occupational Therapy in Pediatrics. 1983;**3**(1):53-57

[5] Ahrendt L. The influence of water programs on infants' motor development. In: Kamp et al, editors. Advances in Motor Development and Learning in Infancy. Proceedings of the First World Congress on Motor Development and Learning in Infancy. Enschede: Print Partners Ipskamp;2001. pp. 85-88

[6] Getz M et al. Effects of aquatic interventions in children with neuromotor impairments: A systematic review of the literature. Clinical Rehabilitation. 2006a;**20**(11):927-937

[7] Goksor E et al. Bradycardic response during submersion in infant swimming. Acta Paediatrica. 2002;**91**(3):307-312

[8] Sweeney JK. Neonatal hydrotherapy: An adjunct to developmental intervention in an intensive care nursery setting. Physical & Occupational Therapy in Pediatrics. 1983;**3**(1):39-52

[9] Stein J. Motor development, the brain, and aquatic therapy. Aquatic Therapy Journal. 2004;**6**(2):19-23

[10] Wilcock D et al. Physiological response to water immersion: A method for sport recovery. Sports Medicine. 2006;**36**(9):747-766

[11] Nordhove SM et al. Early intervention improves behavioral outcomes for preterm infants: Randomized controlled trial. Pediatrics. 2012;**129**:e9

[12] Spittle AJ et al. Improving the outcome of infants born at <30 weeks' gestation – A randomized controlled trial of preventative care at home. BMC Pediatrics. 2009;**9**:73

[13] Orton J et al. Do early intervention programs improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. Developmental Medicine and Child Neurology. 2009;**51**(11):851-859

[14] Guzzetta A et al. The effects of preterm infant massage on brain electrical activity. Developmental Medicine and Child Neurology. 2011

[15] Hernandez-Reif M et al. Preterm infants show reduced stress behaviors and activity after 5 days of massage therapy. Infant Behavior & Development. 2007;**30**:557-561

[16] Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. The Journal of Comparative Neurology. 1990;**297**:441-470

[17] Friedman H et al. Neuroplasticity in young age: Computer-based early

Neurodevelopment and Neurodevelopmental Disease neurodevelopment classifier. Ch. 3. In: Chaban V, editor. Neuroplasticity–Insights of Neural Organization. London, United Kingdom: IntechOpen; 2018

[18] Kostovic I, Judas M. Prolonged coexistence of transient and permanent circuitry elements in the developing cerebral cortex of fetuses and preterm infants. Developmental Medicine and Child Neurology. 2006;**48**:388-393

[19] Luhmann HJ, Kilb W, Hanganu-Opatz IL. Subplate cells: Amplifiers of neuronal activity in the developing cerebral cortex. Frontiers in Neuroanatomy. 2009;**3**(19):1-12

[20] Kanold PO, Luhmann HJ. The subplate and early cortical circuits. Annual Review of Neuroscience. 2010; **33**:23-48

[21] Voigt T, Opitz T, De Lima AD. Synchronous oscillatory activity in immature cortical network is driven by GABAergic preplate neurons. The Journal of Neuroscience. 2001;**21**(22): 8895-8905

[22] Yang JW, Hanganu-Opatz IL, Sun JJ, Luhmann HJ. Three patterns of oscillatory activity differentially synchronize developing neocortical networks in vivo. The Journal of Neuroscience. 2009;**29**:9011-9025

[23] Zhao C, Kao JP, Kanold PO. Functional excitatory microcircuits in neonatal cortex connect thalamus and layer 4. The Journal of Neuroscience. 2009;**29**(49):15479-15488

[24] Hirsch S, Luhmann HJ. Pathway-specificity in N-methyl-d-aspartate receptor-mediated synaptic inputs onto subplate neurons. Neuroscience. 2008; **153**:1092-1102

[25] Kanold PO, Kara P, Reid RC, Shatz CJ. Role of subplate neurons in functional maturation of visual cortical columns. Science. 2003;**301**:521-525

[26] Kanold PO, Shatz CJ. Subplate neurons regulate maturation of cortical inhibition and outcome of ocular dominance plasticity. Neuron. 2006;**51**: 627-638

[27] Perkins L, Hughes E, Srinivasan L, et al. Exploring cortical subplate evolution using MRI of the fetal brain. Developmental Neuroscience. 2008;**30**: 211-220

[28] Allen MC. Neurodevelopmental outcomes of preterm infants. Current Opinion in Neurology. 2008;**21**(2):123

[29] Bassan H et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. Pediatrics. 2007;**120**(4):785-792

[30] Kiechl-Kohlendorfer U et al. Adverse neurodevelopmental outcome in preterm infants: Risk factor profiles for different gestational ages. Acta Paediatrica. 2009;**98**(5):792-796

[31] Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: A review. Seminars in Perinatology. 2006;**30**(2): 81-88

[32] Roze E et al. Functional outcome at school age of preterm infants with periventricular hemorrhagic infarction. Pediatrics. 2009;**123**(6):1493-1500

[33] Volpe JJ. Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. Lancet Neurology. 2009; **8**(1):110-124

[34] Woodward LJ et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. The New England

Journal of Medicine. 2006;**355**(7): 685-694

[35] Han TR, Bang MS, Lim JY, Yoon BH, Kim IW. Risk factors of cerebral palsy in preterm infants. American Journal of Physical Medicine & Rehabilitation. 2002;**81**(4):297-303

[36] Volpe JJ. Cerebral White matter injury of the preterm infant-more common than you thinks (commentaries). Pediatrics. 2003;**112**: 176-180

[37] Larroque B, Ancel PY, Marret S, Marchand L, André M, Arnaud C, et al. EPIPAGE Study group. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): A longitudinal cohort study. Lancet. 2008;**371**(9615): 813-820

[38] Smyser CD, Snyder AZ, Shimony JS, Mitra A, Inder TE, Neil JJ. Resting-state network complexity and magnitude are reduced in prematurely born infants. Cerebral Cortex. 2016; **26**(1):322-333

[39] Fischi-Gómez E, Vasung L, Meskaldji DE, Lazeyras F, Borradori-Tolsa C, Hagmann P, et al. Structural brain connectivity in school-age preterm infants provides evidence for impaired networks relevant for higher order cognitive skills and social cognition. Cerebral Cortex. 2014;**25**(9): 2793-2805

[40] Salmaso N, Jablonska B, Scafidi J, Vaccarino FM, Gallo V. Neurobiology of premature brain injury. Nature Neuroscience. 2014;**17**(3):341-346

[41] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 2000

[42] Kanner L. Autistic disturbances of affective contact. The Nervous Child. 1943;**2**:217-250

[43] Kanner L, Lesser LI. Early infantile autism. Pediatric Clinics of North America. 1958;**5**:711-730

[44] Asperger H. Die "Autistischen Psychopathen" im Kindesalter. Archiv für Psychiatrie und Nervenkrankheiten. 1944;**117**:132-135

[45] Damasio AR, Maurer RG. A neurological model for childhood autism. Archives of Neurology. 1978;**35**: 777-786

[46] Nebel MB, Joel SE, Muschelli J, Barber AD, Caffo BS, Pekar JJ, et al. Disruption of functional organization within the primary motor cortex in children with autism. Human Brain Mapping. 2012. Available online at: http://onlinelibrary.wiley.com

[47] Cossu G, Boria S, Copioli C, Bracceschi R, Giuberti V, Santelli E, et al. Motor representation of actions in children with autism. PLoS ONE. 2012; **7**:e44779

[48] Haswell CC, Izawa J, Dowell L, Mostofsky S, Shadmehr R. Representation of internal models of action in the autistic brain. Nature Neuroscience. 2009;**12**:970-972

[49] Hilton CL, Zhang Y, Whilte MR, Klohr CL, Constantino J. Motor impairment in sibling pairs concordant and discordant for ASDs. Autism. 2012; **16**(4):430-441

[50] Green D, Charman T, Pickles A, Chandler S, Loucas T, Simonoff E, et al. Impairment in movement skills of children with autistic spectrum disorders. Developmental Medicine and Child Neurology. 2009;**51**:311-316

[51] Dowell LR, Mahone EM, Mostofsky SH. Associations of postural knowledge

and basic motor skill with dyspraxia in autism: Implication for abnormalities in distributed connectivity and motor learning. Neuropsychology. 2009;**23**(5): 563-570

[52] Esposito G, Pasca SP. Motor abnormalities as a putative endophenotype for autism spectrum disorders. Frontiers in Integrative Neuroscience. 2013;**7**:43

[53] De Jong M, Punt M, De Groot E, Minderaa RB, Hadders-Algra M. Minor neurological dysfunction in children with autism spectrum disorder. Developmental Medicine and Child Neurology. 2011;**53**(7):641-646

[54] Freitag CM. The genetics of autistic disorders and its clinical relevance: A review of the literature. Molecular Psychiatry. 2007;**12**:2-22

[55] Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. JAMA. 2001;**285**: 3093-3099

[56] Wing L, Potter D. The epidemiology of autistic spectrum disorders: Is the prevalence rising. Mental Retardation and Developmental Disabilities Research Reviews. 2002;**8**:151-161

[57] CDC Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders–Autism and developmental disabilities monitoring network. MMWR Surveillance Summaries. 2006;**58**:1-20

[58] Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics. 2011;**128**:883-891

[59] Movsas TZ, Paneth N. The effect of gestational age on symptom severity in children with autism spectrum disorder. Journal of Autism and Developmental Disorders. 2012;**42**:2431-2439

[60] Matson JL, Kozlowski AM. The increasing prevalence of autism spectrum disorders. Research in Autism Spectrum Disorder. 2011;**5**:418-425

[61] Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: A review and integration of findings. Archives of Pediatrics & Adolescent Medicine. 2007;**161**:326-333

[62] Schendel DE, Autry A, Wines R, Moore C. The co-occurrence of autism and birth defects: Prevalence and risk in a population-based cohort. Developmental Medicine and Child Neurology. 2009;**51**:779-786

[63] Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child: Care, Health and Development. 2008a;**34**:249-256

[64] Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparen P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity. Pediatrics. 2009;**124**:e817-e825

[65] Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstetricia et Gynecologica Scandinavica. 2012;**91**:287-300

[66] Lampi KM, Lehtonen L, Tran PL, Suominen A, Lehti V, Banerjee PN, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. The Journal of Pediatrics. 2012;**161**:830-836

[67] Kalkbrenner et al. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. Epidemiology. 2015;**26**(1):30-42

[68] Dietert RR, Dietert JM, DeWitt JC. Environmental risk factors for autism.

Emerging Health Threats Journal. 2011; **4**:1-11

[69] Meldrum SJ, Strunk T, Currie A, Prescott SL, Simmer K, Whitehouse AJ. Autism spectrum disorder in children born preterm-role of exposure to perinatal inflammation. Frontiers in Neuroscience. 2013;**22**(7):123

[70] Goines PE, Ashwood P. Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment. Neurotoxicology and Teratology. 2013;**36**:67-81

[71] Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biological Psychiatry. 2010;**68**:368-376

[72] Lintas C, Altieri L, Lombardi F, Sacco R, Persico AM. Association of autism with polyomavirus infection in postmortem brains. Journal of Neurovirology. 2010;**16**:141-149

[73] Groen SE et al. General movements in early infancy predict neuromotor development at 9 to 12 years of age. Developmental Medicine and Child Neurology. 2005;**47**(11):731-738

[74] Hadders-Algra M. General Movements: A window for early identification of children at high risk for developmental disorders. Journal of Pediatrics. 2004;**145**:S12-S18

[75] Burger et al. General movements as a predictive tool of the neurological outcome in very low and extremely low birth weight infants–A South African perspective. Early Human Development. 2011;**87**(4):303-308

[76] Harrison P, Oakland T. Adaptive Behavioral Assessment Scale. 2nd ed. San Antonio, Texas, USA: The Psychological Corporation; 2003

[77] Shapiro F. Eye Movement Desensitization and Reprocessing (EMDR). Basic Principles, Protocols and Procedures. 2nd ed. NY, USA: The Guilford Press; 2001