July 2012

Kopf Carrier #74

KOPF CARRIER

PUBLISHED BY DAVID KOPF INSTRUMENTS ■ TUJUNGA, CALIFORNIA

Neuroscience Reviews: Focus On Autism

Edlira Yzeiraj, Brian H. Hallas, German Torres,
Department of Neuroscience and Histology,
New York College of Osteopathic Medicine of New York Institute of Technology,
New York 11568, USA

Corresponding Author: German Torres, Ph.D.,
Department of Neuroscience and Histology,
New York College of Osteopathic Medicine of New York Institute of Technology,
New York 11568, USA, E-Mail: torresg@nyit.edu, Telephone: 516-686-3806

Brain disorders, including developmental, psychiatric and neurodegenerative diseases affect millions of individuals worldwide. In addition to the human suffering they cause, brain disorders also carry significant economic costs in terms of lost earnings, direct health care costs and disability benefits. For example, autism and Autism Spectrum Disorders (ASDs) represent an enormous disease burden with estimates of $3.2 million lifetime cost per case which easily translates to $35 billion per year in the US alone (Ganz, 2007). Obviously, better screening methods for ASDs might lead to substantially higher estimates of disease burden in the near future. Against this background, this brief essay summarizes recent attempts to understand the pathophysiology of autism including, treatments available for this particular developmental disease and our current ability to properly diagnose autism.

Diagnostic Criteria for Autism

Autism and ASDs are currently estimated to affect 1 in 88 children in the US, with male children more commonly affected than female children at a ratio of 4 to 1, respectively (Centers for Disease Control, 2012). Although proposed diagnostic criteria for the disease are still shrouded in controversy, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; to be released 2013) for autism advocates that autistic disorder, Asperger's disorder, childhood disintegrative disorder and pervasive developmental disorder be grouped into a single diagnosis. Under these criteria, the aforementioned four disorders would represent a continuum from mild to severe forms of cognitive disability; in other words, all four disorder phenotypes would be considered a variation of autism.

Firm diagnoses for autism are currently made in children after the age of two and the clinical presentation of the disease are usually characterized by deficits in social interaction, verbal communication, motor skills and by restricted and repetitive behaviors. It is thought, for instance, that autistic children have difficulty identifying emotions and understanding feelings (e.g., anger, fear, happiness) in other's faces, which likely contributes to the development of inadequate social skills. Children with autism also have motor impairments such as running, throwing an object and other motor coordination skills (e.g., learning how to write)

which may be part of the clinical diagnosis (Hilton et al., 2012). From this point of view, a myriad of cognitive and motor disabilities, each with exceptional complexity, describes autistic disorder and related diseases. Thus, children with autism are catalogued (in most cases by the Autism Diagnostic Observation Schedule) according to their relevant symptoms and behaviors which may arise from different underlying causes.

Neurodevelopmental Pathogenesis

It is now well established that autism is a neurodevelopmental disorder with a complex inheritance pattern of several genes that substantially increases the probability of disease onset. For example, patterns of brain development in the first two years of life appear to grow more rapidly in children who are later diagnosed with autistic disorder than their matched-control counterparts who do not developed ASDs. More specifically, brain white matter (i.e., myelin fiber tracts), the conduit that provides the network for chemical communication between synapses, is precociously present in disease-prone children at 6 months of age (Wolff et al., 2012). However, this pattern of rapid brain development unexpectedly halts

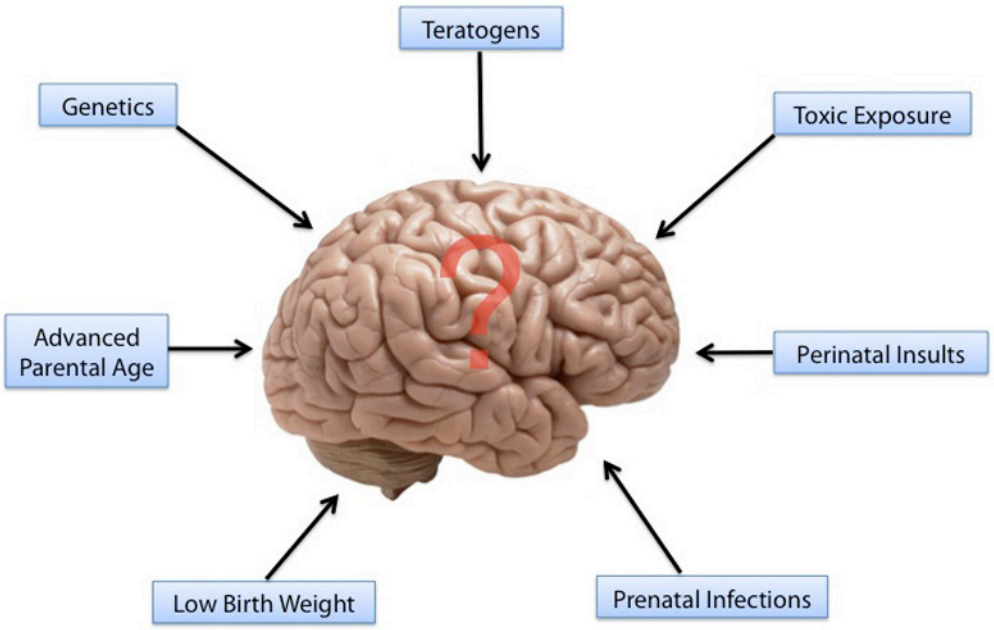

Fig. 1. Biological and environmental factors that may contribute to autism and ASDs. These brain pathologies are characterized by varied deficits in socialization, communication and behavior. Biological factors include mutations in the *Shank2* gene (Leblond et al., 2012). This particular gene encodes a scaffolding protein that helps stabilize synapses between neurons. There is also evidence of duplications and deletions in autistic DNA known as copy-number variants (Leblond et al., 2012). Environmental factors include low birth weight which may affect neuronal spurt growth, and older maternal and paternal age (Rahbar et al., 2012). Prenatal infections and other insults during brain development could either independently or in interaction with autism risk genes precipitate disease onset. Environmental toxins (McCanlies et al., 2012) and, as of yet, unidentified teratogens could also indirectly reduce the number of synapses in the developing brain. These data suggest that autism has multiple biological and environmental underpinnings.

by 24 months of age, leaving behind synaptic lags throughout the brain parenchyma (Wolff et al., 2012). Indeed, structural changes in the way neurons make long-distance connections between the two hemispheres also tend to be in short supply in Timothy Syndrome patients. Affected children display symptoms of ASDs and in addition to showing decreased size of the corpus callosum, Timothy Syndrome neurons release more dopamine and norepinephrine molecules than do control neurons (Pasca et al., 2011). These findings add to previous magnetic resonance imaging (MRI) studies showing that high-functioning patients with ASDs also exhibit disorganized axonal pathways in the corpus callosum and in brain sites involved in spoken language and social skills (Peters et al., 2012). Further, children with Rett Syndrome, another disease with autism-like symptoms, show deficits in the number of dendritic spines or protrusions that help establish synapses in the cortex (Marchetto et al., 2010). Collectively, these data suggest that at least some phenotypes of ASDs arise from defects in the connectivity between developing neurons and their respective synapses. These data also indicate that accelerated head growth (as analyzed by head circumference) and general abnormal brain enlargement appear to be specific to children with ASDs, particularly male children with regressive types of autism (Nordahl et al., 2012). It should be noted that the above neuropathologies do not appear suddenly

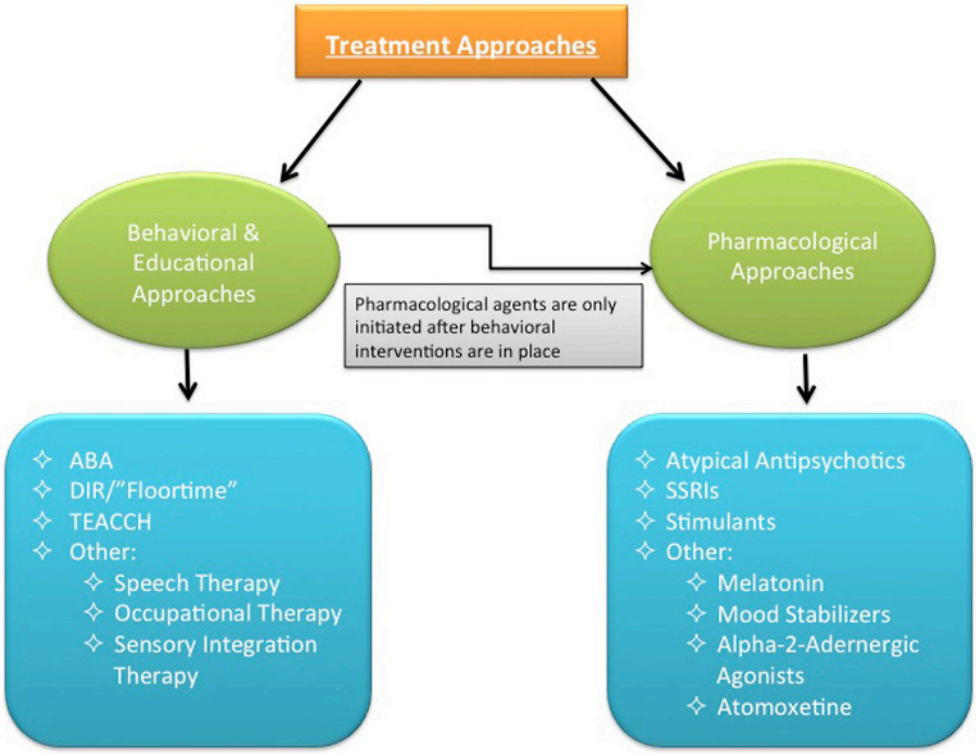

Fig. 2. Current available treatments for autism and ASDs. Because the clinical manifestations of autism vary in severity, treatment must be tailored according to diagnosis. Behavioral and educational approaches (i.e., non-pharmacological therapies) are usually prescribed first to improve social and communication skills. Pharmacological approaches involve the use of atypical antipsychotic and off-labeled drugs. These pharmacological agents are used to target specific behavioral symptoms that are clearly diagnosed. Example of stimulants: Methylphenidate (Ritalin). SSRIs: Selective serotonin re-uptake inhibitors. Melatonin: A pineal hormone used for sleep onset and sleep maintenance; sleep disturbances are often catalogued in children with ASDs. Example of mood stabilizers: Lithium which is used to treat repetitive behaviors and anxiety.

in autistic children, but rather develop during infancy raising the possibility of therapy intervention during the progression phase of the disease. Obviously, we cannot exclude the possibility that environmental risk factors might be linked to having a child with autism.

For example, ill-timed infections during pregnancy, nutritional deficits during certain milestones of brain development, low birth weight or older parental age could all contribute to disease onset and disease progression (Fig. 1).

Pharmacological and Non-Pharmacology Approaches to Autism

Because autism and ASDs have broad set of causes with common behavioral deficits, current therapeutic interventions are also multifactorial in nature (Fig. 2). It should be noted that pharmacological approaches to autism do not directly treat the core features of the disease, but rather its varied clinical symptoms. In the US, drug treatment for ASDs is usually implemented after educational support has failed to improve behavioral outcome or as adjunct therapy to behavioral intervention (Weisman and Bridgemohan et al., 2012). Either way, only the atypical antipsychotic agents, risperidone and aripiprazole are currently approved by the FDA for use in autism and ASDs. Risperidone targets the dopamine, norepinephrine, serotonin and histamine systems of the brain and is commonly prescribed for autistic children with disruptive behaviors including, aggression, explosive outbursts and self-injury (Weisman and Bridgemohan et al., 2012). Aripiprazole also targets the aforementioned neurochemical systems and is recommended for autistic children with irritability, stereotypy and hyperactivity symptoms (Weisman and Bridgemohan et al., 2012). Off-labeled drugs are also used for the treatment of autism and often include α-2-adrenergic agonists (e.g., clonidine), norepinephrine and dopamine re-uptake inhibitors (e.g., atomoxetine and methylphenidate) and selective serotonin re-uptake inhibitors (e.g., fluoxetine and sertraline). Of potential interest to adults with ASDs, the antidepressant fluoxetine appears to diminish restricted, repetitive behaviors (e.g., compulsive and rigid adherence to routines) that interfere with overall functioning and considerably limit quality of life (Hollander et al., 2011). It is important to point out that drugs that target the core features of autism are still far off from current clinical practice and more research, particularly those linked to specific defects of the synapse and its proteins are warranted before the development of more-effective therapeutic interventions become available.

When it comes to behavioral (i.e., non-pharmacological approaches) and environmental interventions for children with autism, there is, as of yet, no single or best therapy. All behavioral therapies aim to maximize cognitive functioning, and teach the patient to become more independent and improve the quality of life for both the child and his/her family. The TEACCH (Treatment and Education of Autistic and Related-Handicapped Children) method, for instance, focuses on organizing the physical environment of the child and developing social communication and cognitive abilities with flexible, scheduled routines (Weisman and Bridgemohan et al., 2012). Applied Behavior Analysis (ABA), on the other hand, aims to teach new skills and to reinforce those already learned by breaking them down to their simplest form (Weisman and Bridgemohan et al., 2012). Thus, this particular method of behavior modification focuses on reinforcing desired behaviors while eliminating those behaviors that are incongruent with social norms or expectations. The DIR (Development, Individual Differences, Relationship-Based Approach; also called Floor-time) aims to develop feelings and relationships with caregivers and to teach the autistic child how to deal with sights, sounds and smells in his/her environment. In general, behavioral therapies for autism have con-

siderably improved since Leon Kanner first described the disease in 1943. Further, behavioral therapies for autism have "borrowed" therapies from other neurodevelopmental disorders such as those currently implemented for children with bipolar disorder and children with Fragile X syndrome. Of particular interest, about a third of boys with Fragile X syndrome are also diagnosed with ASDs and both disorders share some core, behavioral elements (Goebel-Goody and Lombroso 2012). In fact, a number of additional pathologies go hand-in-hand with autism: Endogenous depression and attention deficit hyperactive disorder, for instance. This suggests that disparate disease genotypes could lead to the same ASDs diagnosis. Hopefully, research on the commonalities of these brain diseases will help identify causes and treatments for autism in general.

References

Autism Spectrum Disorders (ASDs). 2011. Centers for Disease Control and Prevention. Autism. Retrieved from www.cdc.gov/ncbddd/autism/

Ganz, ML. 2007. The lifetime distribution of the incremental societal costs of autism. *Arch Pediatr Adolesc Med.* 161(4):343-9.

Goebel-Goody SM, Lombroso PJ . 2012. Taking STEPs forward to understand fragile X syndrome. *Results Probl Cell Differ.* 54:223-41.

Hilton CL, Zhang Y, White MR, Klohr CL, Constantino J. 2012. Motor Impairment in Sibling Pairs Concordant and Discordant for Autism Spectrum Disorders. Autism. [Epub ahead of print].

Hollander E, Soorya L, Chaplin W, Anagnostou E, Taylor BP, Ferretti CJ, Wasserman S, Swanson E, Settipani C. 2011. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult Autism Spectrum Disorders. *Am J Psychiatry* AiA :1 –8.

Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, et al. 2012. Genetic and functional analyses of Shank2 mutations suggest a multiple hit model of Autism Spectrum Disorder. *PLoS Genet* 8(2): e1002521.

Marchetto MC, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. 2010. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell.* 143(4):527-39.

McCanlies EC, Fekedulegn D, Mnatsakanova A, Burchfiel CM, Sanderson WT, Charles LE, Hertz-Picciotto I. 2012. Parental occupational exposures and Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders.* DOI: 10.1007/s10803-012-1468-1.

Nordahl CW, Scholz R, Yang X, Buonocore MH, Simon T, Rogers S, Amaral DG. 2012. Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Arch Gen Psychiatry.* 69(1):53-61.

Rahbar MH , Samms-Vaughan M, Loveland KA, Pearson DA, Bressler J, Chen Z, Ardjomand-Hessabi M, Shakespeare-Pellington S, Grove ML, Beecher C. 2012. Maternal and paternal age are jointly associated with childhood autism in Jamaica. *Journal of Autism and Developmental Disorders.* DOI: 10.1007/s10803-011-1438-z.

Paşca SP, Portmann T, Voineagu I, Yazawa M, Shcheglovitov A, Paşca AM, Cord B, Palmer TD, Chikahisa S, Nishino S, Bernstein JA, Hallmayer J, Geschwind DH, Dolmetsch RE. 2011.Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nat Med.* 17(12):1657-62.

Peters JM, Sahin M, Vogel-Farley VK, Jeste SS, Nelson CA 3rd, Gregas MC, Prabhu SP, Scherrer B, Warfield SK. 2012. Loss of white matter microstructural integrity is as-

sociated with adverse neurological outcome in tuberous sclerosis complex. *Acad Radiol.*19(1):17-25.

Weissman L, Bridgemohan C. 2012. Autism spectrum disorders in children and adolescents: Behavioral and educational interventions. In: UpToDate, Mary M Torchia (Ed), UpToDate, Waltham, MA.

Weissman L, Bridgemohan C. 2012. Autism spectrum disorders in children and adolescents: Pharmacologic interventions. In: UpToDate, Mary M Torchia (Ed), *UpToDate*, Waltham, MA.

Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, Botteron KN, Dager SR, Dawson G, Estes AM, Evans AC, Hazlett HC, Kostopoulos P, McKinstry RC, Paterson SJ, Schultz RT, Zwaigenbaum L, Piven J. 2012. Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism. *Am J Psychiatry.* [Epub ahead of print].

Bibliographies

Edlira Yzeiraj, (eyzeiraj@nyit.edu) OMSIII, received her B.A. in Political Science from Queens College, City University of New York in January 2007. She is currently enrolled at the New York College of Osteopathic Medicine (NYCOM) acting as an Academic Scholar in the Department of Neuroscience and Histology and will graduate in May 2014.

Dr. Brian H. Hallas (bhallas@nyit.edu) received his Ph.D. in neurobiology from Purdue University in 1979. He also holds an M.S. in biology from Purdue University, a B.A. in Psychology, and a B.S. in Biology from University of Hartford. He has been awarded numerous research grants and has authored many articles in scientific journals. He is the recipient of various honors and awards, most recently the prestigious Presidential Service Award from New York Institute of Technology in 2007. In 2004, he was awarded a fellowship by the Heritage Foundation Health Policy for Research in Health Policy based on stem cell research. From 2003 to 2007, he was Associate Dean of Research at the New York College of Osteopathic Medicine of New York Institute of Technology, where he is currently Chair and Professor of the Department of Neuroscience and Histology. He has published over 70 peer reviewed articles, several book chapters and 225 abstracts.

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Neuroscience and Histology at the New York College of Medicine of New York Institute of Technology. His specific research interests are centered on the biological basis of brain disorders.

Contact Information:

New York College of Osteopathic Medicine
of New York Institute of Technology,
Northern Blvd.
Old Westbury, NY 11568
(516) 686-3806.

Editor's Column

This issue, the 74th, of the Kopf *Carrier* introduces a new feature, *Neuroscience Reviews*. This new feature will be published regularly in the newsletter and is authored by Brian Hallas, Ph.D. and German Torres, Ph.D. along with guest authors. Both scientists are at the New York College of Osteopathic Medicine of the New York Institute of Technology in Old Westbury, NY. Dr. Hallas is Chair and Professor of the Department of Neuroscience and Histology while Dr. Torres is Associate Professor in the same department. They have authored several previous *Carrier* articles and will bring their expertise to bear on numerous areas of interest to the neuroscience community in the future. Both are active members of the Society for Neuroscience and have extensive publication histories.

On a personal note, I have known both Brian and German for many years and respect the wide range of interests both have. Brian is an avid fisherman and outdoorsman, while German is an avid reader. I know that their reviews will be both informative and enlightening as they appear.

Here in Florida, it is summer and the rainy season began early this year. In fact, northern Florida was recently inundated with about 19 inches of rain is a couple days. Fortunately, we missed that deluge, but the rains have completely reversed the drought conditions that had been in effect here. That is good news, although it also means that the humidity is high and the mosquitoes are multiplying. We have already had one tropical storm that developed even before the hurricane season began on June 1, but it just dumped a lot of rain on the northeastern part of Florida and Georgia before blowing out to sea from whence it came. We hope this does not mean that the hurricane season will be much more active than usual. So far, so good.

While the next Society for Neuroscience meeting is almost 4 months away, it is not too early to begin planning for it. Since it will be held in New Orleans, it will be an unusually fun and productive time. As many recall, the last time the Society was slated to go to New Orleans, the meeting had to be moved due to the devastation of Katrina and the destruction of much of New Orleans. I for one, am looking forward to going back to this wonderful city and seeing how it has recovered. Please make plans to stop by the Kopf Instruments booth #2313 when you are there to chat with us and look at the superb instruments that will be on display in the booth.

If you have any suggestions for reviews by Drs. Hallas and Torres, or want to write an article for the *Carrier*, please do not hesitate to contact me. As always, all back *Carrier* issues are available free at the Kopf website (www.kopfinstruments.com), along with other helpful information such as lists of stereotaxic manuals and author instructions.I

Michael M. Patterson, Ph.D.
Science Editor
David Kopf Instruments
954-288-5518
954-452-6812 (FAX)
drmikep1@me.com