Published in final edited form as:

Med Hypotheses. 2008 ; 70(1): 73–80. doi:10.1016/j.mehy.2007.04.025.

The Minicolumnopathy of Autism: a Link between Migraine and Gastrointestinal Symptoms

Manuel F. Casanova, MD*

Associate Chair for Research and Professor, Department of Psychiatry and Behavioral Sciences, University of Louisville

Abstract

Gastrointestinal symptoms are common medical problems among autistic patients. A leaky gut and viruses have been proposed as possible culprits but evidence for these etiological agents remains elusive. In this article we put forward an alternate etiology: abdominal migraines. Recent postmortem studies in autism indicate the presence of a minicolumnopathy and its relationship to both serotonergic abnormalities and a hyperexcitable cortex. These features of phenomenology are also observed in migraineurs. A putative relationship between autism and migraine is further suggested by similarities in clinical histories and laboratory evidence. Some commonalities include the presence of neuroinflammation, sensory overstimulation (e.g., flickering of fluorescent lights), “food allergies”, benefits from similar diets, and the role of nitric oxide. Abdominal migraine therefore stands as a falsifiable hypothesis with added importance accrued to potential therapeutic interventions.

Keywords

autism; migraine; minicolumns; gastrointestinal symptoms; serotonin; glutamate

“The brain should not be thought of as a hierarchy of organized autonomous structures, each delivering its output to the next level in a linear function, but as a set of complex interacting networks that are in a state of dynamic equilibrium with the brain’s environment. Migraine...can be considered as one result of an upset in this environment.” [1].

Autism is a condition defined by abnormalities in socialization, language, communication, range of interests, and motor behaviors. The CDC reported that 1 in 152 8-year-olds in 14 states surveyed have an Autism Spectrum Disorders [2]. Multiple studies have associated autism to a variety of genetic disorders or syndromes, e.g., Fragile X [3,4], Down [5], Fetal Rubella, Fetal Valproate [6], and Moebius (congenital facial diplegia) [7]. Medical problems commonly raised by children with autism include sleep disturbances, feeding problems, and gastrointestinal complaints. In order to facilitate treatment and address possible etiologic factors these medical concerns have become topics of recent research.

Address correspondence to: Manuel F. Casanova, MD, Gottfried and Gisela Kolb Endowed Chair in Psychiatry, Department of Psychiatry and Behavioral Sciences, 500 South Preston Street, Building 55A, Room#217, Louisville, Kentucky 40292, Tel: +1-502-852-4077, Fax: +1-502-852-4077, E-mail: E-mail: MOCASA02@louisville.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Recent postmortem studies indicate the presence of minicolumnar disturbances in autism [7-9]. To the extent that autism is a minicolumnopathy, core features of the condition should be explained in terms of pathophysiological mechanisms involving this cortical module. A useful pathological construct, when considered in lieu of prevailing paradigms (e.g., loss of Purkinje cells, diminished size of limbic neurons), should provide additional or novel information having functional implications for affected patients (incremental validity). In this regard we consider the explanatory power of a putative minicolumnopathy as applied to the gastrointestinal symptoms commonly reported by autistic patients. It is our contention that in autism a minicolumnopathy provides for both a hyperexcitable cortex and a serotonergic imbalance that manifests itself early in life as abdominal migraines. Indeed, short autobiographical accounts and anecdotal evidence from the medical literature suggests that autistic individuals have an increased prevalence of migraines [10].

Autism as a Minicolumnopathy

The cause of autism remains unknown but the presence of seizures and derangement in multiple higher order cognitive functions suggests a cortical lesion. Although the findings may be argued, neuroimaging and neuropathological studies indicate a dysplastic process that manifests itself occasionally as gross cortical malformations, lamination abnormalities, aberrant positioning of cells, and underdeveloped neurons [3,7,11]. The concurrence of autism spectrum disorders with brainstem dysplastic processes and disruptions of early morphogenetic areas (e.g., limb fields) suggests that the underlying mechanism takes its toll during embryonic development. A time frame of susceptibility has been calculated based on the fact that brief exposures to thalidomide in pregnant women are linked to an increased occurrence of limb teratogenesis, Moebius syndrome, and autism [12]. The geneses of these side effects encompass the 20th through 36th day of gestation [13].

Recent postmortem studies suggest that autism is the result of a minicolumnar disturbance [8]. Minicolumns are a primary motif of structural organization within the isocortex [14]. Their presence antedates other architectural elements of brain parcellation, e.g., synopsis, lamination, gyrification. It is believed that the cortex is autonomously patterned after germinal cells divide symmetrically (E<40 days in primates) to form a protomap (Gk., *prōtos*; first in time) of the cortex within the ventricular zone [15]. Later on during development the germinal cells divide asymmetrically (E= 40-120 days in primates) and define the total number of pyramidal cells within the minicolumns. Areal identity stems from afferent innervation to the cortex (protocortex) [16]. According to the thalidomide model (see above) the time frame that defines the total number of minicolumns (symmetrical divisions, E<40 days) coincides with the window of susceptibility for autism.

Arguably, thalamic innervation binds minicolumns into larger constructs (macrocolumns) with feature extraction properties [17-19]. Minicolumns, groups of minicolumns, macrocolumns and networks of macrocolumns offer different echelons within the human brain whose interconnectivity provides for the emergence of higher cognitive properties [14]. As compared to controls minicolumns in autism are smaller and therefore increased in total numbers per linear length of cortical field surveyed [8]. In these smaller minicolumns the peripheral neuropil space appears affected more than the core cellular compartment. The peripheral neuropil space provides the conduit for the inhibitory pericolumnar surround which accounts for spatial contrast during a stimulus evoked afferent drive [20]. Abnormalities in the vertical flow of pericolumnar inhibition provides for amplification of signals and thus explains, in part, the seizures observed in some autistic patients [14].

A recent postmortem study using an independent sample has expanded the original findings of a minicolumnopathy in autism by describing a reduction in somatic and nucleolar size of

constituent neurons [9]. The pathological changes preferentially affect heteromodal areas of the isocortex with relative preservation of primary or idiotypic regions [21]. The resultant circuitry is biased so as to emphasize short corticocortical connections at the expense of longer ones, e.g. commissural projections [9].

Serotonin and Cortical Modularity

The anatomical basis of the macrocolumn is defined, in part, by the balance of activity between glutamate and serotonin (5HT) neurotransmission [22,23]. Levels of serotonin modulate the density of α -amino-3-hydroxy-5-methylisoxazole-4- propionic acid (AMPA) receptor subtypes [24]. Increased levels of serotonin (facilitated release or decreased reuptake) have an anticonvulsant effect [25,26]. This mechanism of action helps explain the link between epilepsy and depression [26].

Neural network models clarify the relationship between the clinical symptoms of autism, serotonergic abnormalities and narrowed neural columns [27]. These models also indicate an association between narrowed neural columns and deficiencies in nitric oxide [27]. The conclusions from these constructs are supported by a florescent literature on nitric oxide and serotonin interactions. This includes the formation of dimmers and nitro- and nitroso-serotonin, all of which are inactive at modulatory 5HT sites [28,29].

Prenatal exposure to alcohol, selective serotonin reuptake inhibitors, and excess serotonin (monoamine oxidase inhibitors [MAO-A] and MAO-A knockout mice) deleteriously affect the postnatal development of cortical barrel formation [23,30]. The effects appear to be mediated by the transient expression of functional serotonin transporter in the axons of thalamocortical fibers. Knock-out mice for the serotonin transporter show a complete lack of macrocolumnar structures (barrels) despite no visible alterations in either the density of synapses or the length of synaptic contacts in layer IV [31]. Serotonergic projections to the marginal zone make synaptic contacts with Cajal-Retzius cells. Disturbing the normal development of these connections lowers reelin levels and alters columnar development [32]. Some of these early effects of serotonin on cortical modularity may unfold during protracted periods of time as sub-compartmentalization of macrocolumnar organization is a process that occurs gradually during the postnatal period [33].

Serotonin and Cortical Hyperexcitability

Autism

It has been hypothesized that in the presence of normal-sized thalamocortical terminal fields the smaller minicolumns observed in autism provide for an overabundance of these modules within any given macrocolumn [8]. The resultant excess of minicolumns would require an increase of inhibitory tone (e.g. serotonin, see above) to balance the physiology of the cortex. In effect, alterations in the capacity of the brain to synthesize serotonin have been reported in autistic children using positron emission tomography [34]. Peripheral serotonergic biomarkers exhibit abnormalities similar to those reported in the brain, e.g., platelet serotonin is increased in approximately one third of autistic patients [35-39]. After controlling for racial and pubertal effects autistic patients have a 25% mean increase in blood serotonin levels [40]. The increased whole blood serotonin is found not only in autistic patients but also in first degree relatives [37,41]. Platelet serotonin is exogenously derived and taken within cells by an active transport mechanism. In autism multiple lines of evidence suggest that platelets are not exposed to increased concentrations of serotonin but, rather, seem to mishandle this chemical [42].

Some of the behavioral symptoms of autism, specifically the repetitive behaviors, are strongly related to serotonergic (5HT) dysfunction [43]. It has also been reported that Sumatriptan, a 5-

HT1d receptor agonist and an antimigraine medication, improved symptoms of autism and migraine in patients who suffered from both disorders [43]. Although Sumatriptan is primarily a 5-HT1d receptor agonist it may also bind to other subtypes of 5HT receptors [44]. Double blind studies of serotonin reuptake inhibitors, clomipramine [45], and fluvoxamine [46] as well as open label studies of fluoxetine [47] and sertraline [48], have documented efficacy in treating various symptoms of autism. Depletion of 5HT precursor tryptophan, have been shown to induce a worsening of autistic symptoms in some but not all patients [49].

We have already discussed how serotonergic abnormalities appear related to epilepsy [25, 26]. It is thus unsurprising that approximately one third of patients with autism suffer from seizures by the time that they reach puberty [7]. The percentage may be higher when considering epileptiform EEG activity regardless of seizure activity [50]. It has been hypothesized that early serotonergic disturbances alter the development of cortical thalamocortical innervation and underlies the pathophysiology of epilepsy in autism [51]. Cortical hyperexcitability and serotonergic abnormalities are therefore well established and interrelated features of autistic phenomenology.

Migraine

The large majority of the body's serotonin is found in the enterochromaffin cells of the gut. Serotonin is released from the gut to the bloodstream but serum levels are kept low by uptake into platelets [1]. In migraineurs there is a deficit in uptake kinetic of serotonin by platelets that accounts for abnormal levels of this chemical. During the headache phase there is a fall in blood levels of serotonin and an increase in its metabolites in both plasma and urine [1].

Modern pharmacological interventions for migraine started with subcutaneous ergotamine, a powerful alkaloid vasoconstrictor. Later on serotonin, a potent vasoconstrictor, was shown to be released from platelets during migraine attacks. Current management of migraine includes serotonergic agonists during acute episodes and the use of serotonergic antagonists and anticonvulsants as migraine prophylactics [1,52,53]. A therapeutic response to anticonvulsant therapy has been noted in case reports and series of children with abdominal migraine and epileptiform discharges [54,55].

A hyperexcitable cortex and increased serotonin are characteristic of migraine [56]. Epileptiform activity, including spike and wave patterns, has been reported in patients during migraine attacks [57]. It has been argued that the visual discomfort and illusions of migraineurs are a manifestation of their hyperexcitable cortex. Although results have been inconsistent there appears to be a reduced threshold for the induction of visual auras by transcranial magnetic stimulation and reduced latencies and increased amplitude responses to evoked potentials [58]. The mechanism underlying cortical hyperexcitability in migraine is unknown but may be related to increased levels of cerebrospinal glutamate and reduced brain levels of Mg^{2+} [59, 60].

Clinical History

Autism

It is well established that autistic individuals sometimes respond in an unusual manner to sensory stimuli. The hum of a vacuum cleaner or the school bell's ringing can hurt their ears and provide for pathological anxiety. Temple Grandin [61] describes a lady who could not tolerate a baby's crying, even when she was wearing both earplugs and earmuffs. She also describes from self-experience stiffening up and pulling away when people hugged her. The needs to desensitize, relax, and tolerate touch led Temple Grandin [61] to build a pressure

machine. The fact that such experiences tend to generalize among autistic subjects have led other researchers to implement treatments such as auditory and sensory integration therapies.

Sensory processing abnormalities are correlated with higher levels of repetitive and stereotypical behaviors. From a behaviorist standpoint some autistic symptoms represent an avoidance reaction to overstimulation [62]. This reasoning has important implications for treatment. Indeed, occasional autistic tantrums are best handled by diminishing all sources of stimulation; e.g., going into a room and closing all windows, turning off the light, etc. Visual overload is a common phenomenon in autism, especially troublesome is the flickering of fluorescent lights. Transitional prism lenses modify distortions of ambient vision. Their use has also been shown to diminish behavioral problems in a double-blind crossover study of autistic patients [63]. Many of these patients are photosensitive and experience some benefit from wearing photoreactive lenses [64,65].

Autistic patients similar to migraineurs react strongly to smells and have peculiarities in terms of food intake. Furthermore migraine-like equivalents have been described in young children with autism, e.g. abdominal pain. Some investigators speak about a gastroenteritis of autism [66] due to the high incidence (approximately 19%) of gastrointestinal problems in this population [67]. Esophagitis and duodenitis were described in almost two thirds of the symptomatic children brought for endoscopy. Findings of lymphoid nodular hyperplasia from biopsied specimens of autistic children have been controversial as several of the coauthors from the original study by Wakefield and associates (1998)[68] have retracted their conclusions and renounced the findings [69]. Lymphoid nodular hyperplasia has been found in conditions other than autism, including allergies [70]. At least two series of nonautistic children having colonoscopy for gastrointestinal symptoms have reported lymphoid nodular hyperplasia in 46 out of 140 and in 53 out of 74 cases [66,71]. Treatment includes special diets restricting casein and gluten intake [62]. At least two studies using large samples have reported some benefits from this dietary intervention [72,73]

The underlying pathology of autism is unknown. Recent findings suggest the presence of a minicolumnopathy which could explain many of the signs and symptoms of this condition [9,74]. However, it is sometimes difficult to distinguish primary lesions from secondary features of pathology especially when secondary aspects of pathology are more easily visualized than less conspicuous core features. One example may be the presence of astrocytosis in postmortem brain tissue of autistic individuals when compared to computer generated measures of minicolumnar morphometry [75].

Inflammation is a response to cell injury that involves, among other things, a vascular component. Thus far there has been no evidence of inflammatory changes in either brain or CSF of patients with autism (e.g., cell counts, protein electrophoresis). Recent work by Vargas and associates (2005) [76] has shown that brains of autistic patients have an increased number of astrocytes and microglia in the absence of a vascular component or cellular transmigration. This innate, noninflammatory response of the brain appears to be chronic in nature as suggested by a cytokine profile that includes both inflammatory and anti-inflammatory agents. Similarly, the cytokine profile suggests that involved glia cells appear to be activated. Otherwise, except for increased cell numbers, there is no evidence of glia activation by light microscopy, e.g., astrocytes do not acquire a characteristic gemistocytic appearance nor microglia participate in neurophagia, nodule formation or transform into foam cells. In this regard the pathology is different from other immune mediated disorders of the central nervous system (e.g. Alzheimer's disease, epilepsy, multiple sclerosis) but similar to that reported for migraine (see below).

Migraine

Migraine is a condition entirely diagnosed by clinical history [1]. Diagnostic criteria were provided by the International Headache Society in a series of definitions last revised in 2004 (ICH-2). The inclusion of a “probable migraine” classification within ICH-2 attests to borderline cases where clinical suspicion supercedes the lack of diagnostic criteria. In effect, headache is the most prominent feature of migraine but the underlying pathophysiological mechanisms often cause other systemic manifestations without necessitating a cephalgia. The term “migraine equivalent or variant” is used in these cases where transient organ system dysfunction occurs in some individuals with migraine or familial predisposition to the same [77]. Symptoms include discrete paroxysmal attacks of dizziness/vertigo, abdominal pains, bloating, vomiting (bilious attacks), and diarrhea. These paroxysmal attacks occur in a setting of phonophobia/photophobia and other autonomic symptoms such as pallor and flushing. Symptoms are usually seen in children and young adults with a mean age of onset of 7 years, reaching a peak at age 10 years and thereafter falling rapidly [78]. During attacks patients usually retreat to isolation, choosing to stay in a dark room, remain undisturbed, and avoid their normal activities and human contact.

Abdominal migraine is episodic with recovery between attacks. The differential diagnosis includes episodic abdominal conditions such as biliary disease, partial bowel obstruction and irritable bowel syndrome [79]. Oliver Sacks (1985) [80] has stated that with migraine equivalents “...indeed there is probably no field in medicine so strewn with the debris of misdiagnosis and mistreatment, and of well-intentioned but wholly mistaken medical and surgical interventions” (pages 49 and 50). Least to say the misdiagnosis of migraine equivalents is a common occurrence brought upon by multiple referrals through varied medical specialties.

Foods are usual triggers for abdominal migraine, common culprits include cow’s milk, chocolate, cheese, wheat products, rye, and baked beans [81]. Intolerance to a wide range of foods has led some investigators to suggest that migraine is a food allergy [82]. In a study of 88 children with severe frequent migraine, 93% recovered with an oligoantigenic diet [82]. The study included a challenge phase where provoking foods were introduced one by one causing recurrence of abdominal symptoms. A successful diet requires a wide spectrum diet as the sole exclusion of foods high in tyramine, such as cheese and chocolate provided recovery in only 5% of patients. The same appeared to be true upon the sole avoidance of food colorings and preservatives.

Migraine headaches can be triggered by flickering lights, sounds, dietary factors, and odors. Early writers believed that migraine was caused by toxins connected to abdominal disorders [83,84]. More recently, researchers believe that migraine is generated by normal brain structures in response to abnormal physiological reactions in what has been called a wave of “spreading depression.” Small trauma, toxins, excitatory amino acids, electrical stimuli and nitric oxide donors when applied to the cortex cause a short-lived positive wave of neural excitation followed by a prolonged phase of neural depression and a dramatic failure of brain ion homeostasis [85]. The wave spreads from its origin in all outward directions at a rate of 3 to 5 mm/min. The spread occurs without regards to anatomical boundaries or vascular territories and appears to be mediated by K⁺ homeostasis. Numerous neuroprotective mechanisms counter the spreading wave of depression including increases in the levels of tumor necrosis factor, interleukin 1, and clustering (a protein produced by neurons and activated astrocytes) [86]. Perfusates of sites of migraine headaches possess inflammatory activity proportional to the intensity of the pain [87]. Repeated episodes of cortical spreading depression lead to activation of astrocytes and consequent increased immunocytochemical staining of glial fibrillary acidic protein (GFAP) [88]. The prominent response of innate elements of the brain to the spread of depression and activation of the trigeminovascular system has led some researchers to label migraine as a neuroinflammatory condition [89].

Conclusions

This article espouses the hypothesis that the gastrointestinal complaints of autistic patients are a migraine equivalent. Both autism and migraine are defined by serotonergic abnormalities and a hyperexcitable cortex. Other commonalities exist in regards to clinical history and laboratory findings making the hypothesis empirically meaningful. Difficulties in establishing a relationship stem from the fact that diagnostic criteria for migraine rely exclusively on a good history. Autistic patients have deficits in language development which makes it difficult for them to communicate symptoms. However, electrophysiological methods may bypass history and provide for outcome measures making the hypothesis falsifiable. In this regards methods such as transcranial magnetic stimulation (TMS) may simultaneously provide for outcome measures of cortical hyperexcitability and provide for potential interventions [90].

The discovery of hyperserotonemia in 1961 by Schain and Freedman gave rise to a putative intervention with a drug that causes the long term depletion of serotonin: fenfluramine. After some promising results [91], the drug showed great variability of effects and no improvements in large clinical trials. Ultimately the drug was withdrawn from the US market after reports of some serious side effects that included heart valve disease, pulmonary hypertension and cardiac fibrosis. It is thus important to cautiously consider any conclusions before translating findings into clinical trials, e.g. serotonergic drugs and nitric oxide synthase inhibitors. According to the mechanisms presented in this article these attempts would be directed towards secondary aspects of pathology and not the core features of the condition (minicolumnopathy). Such attempts provide an opportunity for symptomatic treatment but otherwise remain far removed from providing a cure.

Acknowledgments

This work was supported by grant funding from the National Alliance for Autism Research (NAAR) (MFC), and NIH grant numbers MH62654 and MH69991.

References

1. Lane, R.; Davies, P. *Migraine*. New York, NY: Taylor and Francis; 2006.
2. Rice C. Prevalence of Autism Spectrum Disorders: Autism and Developmental Disabilities monitoring network, six sites, United States, 2000. Center for Disease Control Morbidity and Mortality Weekly Report 2007;56(SS01):1–11.
3. Bailey A, Bolton P, Butler L, Le Couteur A, Murphy M, Scott S, Webb T, Rutter M. Prevalence of the fragile X anomaly amongst autistic twins and singletons. *J Child Psychol Psychiatry* 1993;34(5):673–88. [PubMed: 8340438]
4. Piven J, Gayle J, Landa R, Wzorek M, Folstein S. The prevalence of fragile X in a sample of autistic individuals diagnosed using a standardized interview. *J Am Acad Child Adolesc Psychiatry* 1991;30(5):825–30. [PubMed: 1938801]
5. Kent L, Evans J, Paul M, Sharp M. Comorbidity of autistic spectrum disorders in children with Down syndrome. *Developmental Medicine & Child Neurology* 1999;41(3):153–158. [PubMed: 10210247]
6. Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, Montgomery T, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet* 2000;37(7):489–497. [PubMed: 10882750]
7. Bauman, M.; Kemper, T. *The Neurobiology of Autism*. Vol. 2. Baltimore, MD: The Johns Hopkins University Press; 2005.
8. Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, et al. Minicolumnar pathology in autism. *Neurology* 2002a;58(3):428–432. [PubMed: 11839843]
9. Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, et al. Minicolumnar abnormalities in autism. *Acta Neuropathol (Berl)*. 2006a **Epub ahead of print**
10. Sullivan R. Hunches on some biological factors of autism. *Journal of Autism & Childhood Schizophrenia* 1975;5(2):177–86. [PubMed: 1174120]

11. Piven J, Arndt S, Bailey J, Havercamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. *Am J Psychiatry* 1995;152(8):1145–9. [PubMed: 7625461]
12. Stromland K, Nordin V, Miller M, Akerstrom B, Gillberg C. Autism in thalidomide embryopathy: a population study. *Dev Med Child Neurol* 1994;36(4):351–6. [PubMed: 8157157]
13. Silverman WA. The Schizophrenic Career of a “Monster Drug”. *Pediatrics* 2002;110(2):404–406. [PubMed: 12165600]
14. Casanova MF, Buxhoeveden D, Gomez J. Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autism. *Neuroscientist* 2003;9(6):496–507. [PubMed: 14678582]
15. Rakic P. Specification of cerebral cortical areas. *Science* 1988;241(4862):170–176. [PubMed: 3291116]
16. Chambers D, Fishell G. Functional genomics of early cortex patterning. *Genome Biol* 2006;7(1):202. [PubMed: 16515721]
17. Favorov OV, Diamond ME. Demonstration of discrete place-defined columns--segregates--in the cat SI. *J Comp Neurol* 1990;298(1):97–112. [PubMed: 2212100]
18. Favorov OV, Kelly DG. Minicolumnar organization within somatosensory cortical segregates: I. Development of afferent connections. *Cereb Cortex* 1994;4(4):408–27. [PubMed: 7950312]
19. Mountcastle VB. The columnar organization of the neocortex. *Brain* 1997;120(4):701–722. [PubMed: 9153131]
20. Tommerdahl M, Taman V, Cascio CJ, Baranek GT, Whitsel BL. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. *Brain Res.* 2007
21. Casanova MF, Van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HWM, et al. Abnormalities of Cortical Minicolumnar Organization in the Prefrontal Lobes of Autistic Patients. *Clinical Neuroscience Research.* 2006
22. Blue ME, Johnston MV. The ontogeny of glutamate receptors in rat barrel field cortex. *Developmental Brain Research* 1995;84(1):11. [PubMed: 7720211]
23. Xu Y, Sari Y, Zhou FC. Selective serotonin reuptake inhibitor disrupts organization of thalamocortical somatosensory barrels during development. *Developmental Brain Research* 2004;150(2):151. [PubMed: 15158078]
24. Shutoh F, Hamada S, Shibata M, Narita M, Shiga T, Azmitia EC, et al. Long term depletion of serotonin leads to selective changes in glutamate receptor subunits. *Neuroscience Research* 2000;38(4):365. [PubMed: 11164563]
25. Jobe PC, Browning RA. The serotonergic and noradrenergic effects of antidepressant drugs are anticonvulsant, not proconvulsant. *Epilepsy & Behavior* 2005;7(4):602.
26. Smolders I. Differential glutamatergic modulation of monoamine release in the limbic lobe by selective anticonvulsant ionotropic and metabotropic glutamate receptor ligands. *Verh K Acad Geneesk Belg* 2005;67(56):371–98. [PubMed: 16408832]
27. Gustafsson L. Comment on “Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autism”. *Neuroscientist* 2004;10(3):189–191. [PubMed: 15155057]
28. Fossier P, Blanchard B, Ducrocq C, Leprince C, Tauc L, Baux G, et al. Nitric oxide transforms serotonin into an inactive form and this affects neuromodulation. *Neuroscience* 1999;93(2):597. [PubMed: 10465443]
29. Liese E, Thavaradhara K, Durham NR, Turner BE. Serotonin and nitric oxide regulate metamorphosis in the marine snail *Ilyanassa obsoleta*. *American Zoologist* 2001;41(2):258–267.
30. Powrozek TA, Zhou FC. Effects of prenatal alcohol exposure on the development of the vibrissal somatosensory cortical barrel network. *Developmental Brain Research* 2005;155(2):135. [PubMed: 15804402]
31. Persico AM, Mengual E, Moessner R, Hall SF, Revay RS, Ichiro S, et al. Barrel Pattern Formation Requires Serotonin Uptake by Thalamocortical Afferents, and Not Vesicular Monoamine Release. *J Neurosci* 2001;21(17):6862–6873. [PubMed: 11517274]
32. Janusonis S, Gluncic V, Rakic P. Early Serotonergic Projections to Cajal-Retzius Cells: Relevance for Cortical Development. *J Neurosci* 2004;24(7):1652–1659. [PubMed: 14973240]

33. Louderback K, Glass CS, Shamalla-Hannah L, Erickson SL, Land PW. Subbarrel patterns of thalamocortical innervation in rat somatosensory cortical barrels: Organization and postnatal development. *The Journal of Comparative Neurology* 2006;497(1):32–41. [PubMed: 16680781]
34. Chugani D, Muzik O, Behen M, Rothermel R, Janisse JJ, Lee J, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol* 1999;45(3):287–295. [PubMed: 10072042]
35. Anderson G, Freedman DX, Cohen DJ, Volkmar FR, Hoder EL, McPhedran P, et al. Whole blood serotonin in autistic and normal subjects. *J Child Psychol Psychiatry* 1987;28(6):885–900. [PubMed: 3436995]
36. Anderson G, Horne WC, Chatterjee D, Cohen DJ. The hyperserotonemia of autism. *Ann N Y Acad Sci* 1990;600:331–40. [PubMed: 2252319]
37. Cook EH, Leventhal BL, Freedman DX. Free serotonin in plasma: Autistic children and their first-degree relatives. *Biological Psychiatry* 1988;24(4):488. [PubMed: 3408767]
38. Hoshino Y, Yamamoto T, Kaneko M, Tachibana R, Watanabe M, Ono Y, et al. Blood serotonin and free tryptophan concentration in autistic children. *Neuropsychobiology* 1984;11(1):22–7. [PubMed: 6204248]
39. Schain RF, Freedman DX. Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children. *J Pediatr* 1961;58:315–20.
40. McBride P, Anderson GM, Hertzog ME, Snow ME, Thompson SM, Khait VD, et al. Effects of diagnosis, race, and puberty on platelet serotonin levels in autism and mental retardation. *J Am Acad Child Adolesc Psychiatry* 1998;37(7):767–76. [PubMed: 9666633]
41. Piven J, Tsai GC, Nehme E, Coyle JT, Chase GA, Folstein SE. Platelet serotonin, a possible marker for familial autism. *J Autism Dev Disord* 1991;21(1):51–9. [PubMed: 2037549]
42. Anderson, G. Serotonin in autism. In: Bauman, M.; Kemper, T., editors. *The Neurobiology of Autism*. Johns Hopkins University Press; Baltimore, MD: 2005. p. 303–318.
43. Hollander E, Novotny S, Allen A, Aronowitz B, Cartwright C, DeCaria C. The relationship between repetitive behaviors and growth hormone response to sumatriptan challenge in adult autistic disorder. *Neuropsychopharmacology* 2000;22(2):163–7. [PubMed: 10649829]
44. Adham N, Bard JA, Zgombick JM, Durkin MM, Kucharewicz S, Weinshank RL, et al. Cloning and characterization of the guinea pig 5-HT_{1F} receptor subtype: a comparison of the pharmacological profile to the human species homolog. *Neuropharmacology* 1997;36(45):569–76. [PubMed: 9225282]
45. Gordon C, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* 1993;50(6):441–7. [PubMed: 8498878]
46. McDougall C, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry* 1998;53(11):1001–8. [PubMed: 8911223]
47. Mehlinger R, Scheftner W, Poznanski E. Fluoxetine and autism. *J Am Acad Child Adolesc Psychiatry* 1990;29(6):985. [PubMed: 2273035]
48. Steingard R, Zimnitzky B, DeMaso DR, Bauman ML, Bucci JP. Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. *J Child Adolesc Psychopharmacol* 1997;7(1):9–15. [PubMed: 9192538]
49. McDougall C, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH. Effects of tryptophan depletion in drug-free adults with autistic disorder. *Arch Gen Psychiatry* 1996;53(11):993–1000. [PubMed: 8911222]
50. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy & Behavior* 2006;8(1):267. [PubMed: 16403678]
51. Chugani D. Serotonin in autism and pediatric epilepsies. *Mental Retardation and Developmental Disabilities Research Reviews* 2004;10(2):112–116. [PubMed: 15362166]
52. Arulmozhi D, Veeranjanyulu A, Bodhankar S. Migraine: current therapeutic targets and future avenues. *Curr Vasc Pharmacol* 2006;4(2):117–128. [PubMed: 16611154]

53. Silberstein S. Preventive treatment of migraine. *Rev Neurol Dis* 2005;2(4):167–75. [PubMed: 16622394]
54. Olmez A, Kose G, Turanli G. Cyclic Vomiting With Generalized Epileptiform Discharges Responsive to Topiramate Therapy. *Pediatric Neurology* 2006;35(5):348. [PubMed: 17074606]
55. Tan V, Sahami AR, Peebles R, Shaw RJ. Abdominal Migraine and Treatment With Intravenous Valproic Acid. *Psychosomatics* 2006;47(4):353–355. [PubMed: 16844896]
56. Welch K. Concepts of migraine headache pathogenesis: insights into mechanisms of chronicity and new drug targets. *Neurol Sci* 2003;24(Suppl 2):S149–53. [PubMed: 12811616]
57. Lane R. Migraine and Epilepsy. *Megrim* 1991;4:8–12.
58. Pietrobon D, Striessnig J. Neurobiology of migraine. *Nat Rev Neurosci* 2003;4(5):386–98. [PubMed: 12728266]
59. Ferrari M, Odink J, Bos KD, Malessy MJ, Bruyn GW. Neuroexcitatory plasma amino acids are elevated in migraine. *Neurology* 1990;40(10):1582–6. [PubMed: 1977102]
60. Mauskop A, Altura B. Role of magnesium in the pathogenesis and treatment of migraines. *Clin Neurosci* 1998;5(1):24–7. [PubMed: 9523054]
61. Grandin, T. A personal perspective of Autism. In: Volkmar, F., et al., editors. *Handbook of Autism and Pervasive Developmental Disorders*. John Wiley and Sons; New Jersey: 2005. p. 1276-1286.
62. Schreibman, L. *The Science and Fiction of Autism*. Cambridge, MA: Harvard University Press; 2005.
63. Kaplan M, Edelson S, Seip J. Behavioral changes in autistic individuals as a result of wearing ambient transitional prism lenses. *Child Psychiatry Hum Dev* 1998;29(1):65–76. [PubMed: 9735531]
64. Edelson, S. Scotopic sensitivity syndrome and the Irlen Lens System. 2007. cited; Available from: <http://www.autism.org/irlen.html>
65. Wilkins, A. *Reading through Colour: How coloured filters can reduce reading difficulty, eye strain, and headaches*. Sussex, England: John Wiley and Sons; 2003.
66. Buie, T. Gastrointestinal Issues Encountered in Autism. In: Bauman, M.; Kemper, T., editors. *The Neurobiology of Autism*. Johns Hopkins University Press; Baltimore, MD: 2005. p. 103-117.
67. Fombonne E, Chakrabarti S. No Evidence for A New Variant of Measles-Mumps-Rubella-Induced Autism. *Pediatrics* 2001;108(4):e58. [PubMed: 11581466]
68. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet* 1998;351(9103):637.
69. Murch SH, Anthony A, Casson DH, Malik M, Berelowitz M, Dhillon AP, et al. Retraction of an interpretation. *The Lancet* 2004;363(9411):750.
70. Sabra A, Bellanti J, Colon A. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;352(9123):234–5. [PubMed: 9683237]
71. Kokkonen J, Karttunen T. Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? *J Pediatr Gastroenterol Nutr* 2002;34(1):42–6. [PubMed: 11753163]
72. Knivsberg A, Reichelt KL, Nodland M, Høien T. Autistic syndromes and diet: a follow-up study. *Scandinavian Journal of Educational Research* 1995;39:223–236.
73. Lucarelli S, Frediani T, Zingoni AM, Ferruzzi F, Giardini O, Quintieri F, et al. Food allergy and infantile autism. *Panminerva Medicine* 1995;37(3):137–41.
74. Casanova M, Buxhoeveden D, Brown C. Clinical and macroscopic correlates of minicolumnar pathology in autism. *J Child Neurol* 2002;17(9):692–5. [PubMed: 12503647]
75. Casanova, M.; Switala, AE. Minicolumnar Morphometry: Computerized Image Analysis. In: Casanova, MF., editor. *Neocortical Modularity and the Cell Minicolumns*. Nova Science Publishers, Inc.; New York, NY: 2005. p. 161-180.
76. Vargas D, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology* 2005;57(1):67–81. [PubMed: 15546155]
77. Cullen K, Macdonald W. The periodic syndrome: its nature and prevalence. *Med J Aust* 1963;50(2):167–73. [PubMed: 14024194]

78. Abu-Arafeh I, Russell G. Prevalence and clinical features of abdominal migraine compared with those of migraine headache. *Arch Dis Child* 1995;72(5):413–7. [PubMed: 7618907]
79. Davidoff, R. Contemporary Neurology Series. Oxford University Press; Oxford, England: 2002. Migraine: Manifestations, Pathogenesis, and Management.
80. Sacks, O. Migraine. Berkley, CA: University of California Press; 1985.
81. Symon, D. Equivalents, variants, and precursors of migraine. In: Guidetti, V., editor. Headache and Migraine in Childhood and Adolescence. Martin Dunlitz, LTD; London: 2002. p. 215-227.
82. Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. *Lancet* 1983;2(8355):865–9. [PubMed: 6137694]
83. Isler, H.; Rose, F. Historical Background. In: Olesen, J.; Tfelt-Hansen, P.; Welch, K., editors. The Headaches. Lippincott, Williams, and Wilkins; Philadelphia, PA: 2000. p. 1-7.
84. Rose F. European neurology from its beginnings until the 15th century: an overview. *J Hist Neurosci* 1993;2(1):21–44. [PubMed: 11618442]
85. Lauritzen M. Pathophysiology of the migraine aura: The spreading depression theory. *Brain* 1994;117 (1):199–210. [PubMed: 7908596]
86. Sanchez-del-Rio M, Reuter U. Migraine aura: new information on underlying mechanisms. *Curr Opin Neurol* 2004;17(3):289–93. [PubMed: 15167063]
87. Chapman L, Ramos AO, Goodell H, Silverman G, Wolff HG. A humoral agent implicated in vascular headache of the migraine type. *Arch Neurol* 1960;3:223–9. [PubMed: 13809242]
88. Kraig RP, Dong LM, Thisted R, Jaeger CB. Spreading depression increases immunohistochemical staining of glial fibrillary acidic protein. *J Neurosci* 1991;11(7):2187–2198. [PubMed: 1906091]
89. Spierings, E. Inflammation in migraine pathogenesis: when, where, and how. In: Spierings, E.; Sanchez-del-Rio, M., editors. Migraine: A Neuroinflammatory Disease?. Birkhauser Verlag; Basel: 2002. p. 1-20.
90. Mohammad, Y.; Kothari, R.; Hughes, G.; Nikrumah, M.; Fischell, S.; Fischell, R.; Schweiger, J.; Ruppel, P. Transcranial Magnetic Stimulation (TMS) relieves migraine headache. 48th Annual Scientific Meeting of the American Headache Society (AHS); 2006; Los Angeles.
91. Geller E, Ritvo ER, Freeman BJ, Yuwiler A. Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys. *New Eng J Med* 1982;307(3):165–9. [PubMed: 7088052]