**Chaos, Migraine, and Evolution**

**Lawrence Robbins,M.D., Chicago Medical School**

**Running Head: Chaos, Migraine, and Evolution**

**Correspondence should be addressed to: Lawrence Robbins, 2610 Lake Cook Rd., suite 160, Riverwoods, Ill., 60015,** **lrobb98@icloud.com****, 847-3749399 (f) 847 3749393.**

 **ABSTRACT**

Chaotic dynamics play a role in migraine pathophysiology. Chaos also has been a factor in the dynamics of evolution. Humans remain remarkably vulnerable to migraine, with evolutionary factors being the primary reason.

   The central nervous system, from the ionic level to neural networks, utilizes chaotic dynamics to some degree. Cortical spreading depression, an integral part of migraine with aura, is likely under chaotic control to some degree. Peripheral and central sensitization are primary pathophysiologic processes in the generation of migraine attacks. These also use chaotic dynamics, at least to some degree.

   Chaos, chance, and coincidence are key components of natural selection and evolution. The course of evolution is extremely sensitive to initial conditions, typical for chaotic dynamics. The fractal tree of life follows non-linear dynamics.

   To understand why migraine has persisted in Homo sapiens, we must look through an evolutionary lens. There are a number of genes involved in migraine. Evolution does not possess efficient means with which to delete harmful genes. There may also be a few positive trade-offs with migraine. By paying attention to evolution, we may be able to develop safer and more effective migraine treatments.

**Key Words:** headache, non-linear dynamics, natural selection, neural networks

 **INTRODUCTION**

   Migraine often results in disability and diminished quality of life. Despite this, our species remains particularly vulnerable to migraine. Why is this so?  Evolution may provide answers. The study of evolution and disease is not simply an academic exercise. In studying the history of our species, and those that preceded us, we may be able to develop safer and more effective treatments. We ignore evolution at our peril.

   Chaos theory is a subset of nonlinear dynamics. Nature has been able to utilize chaotic dynamics in the brain, heart, and elsewhere (Korn, & Faure, 2003). Chaotic dynamics provide advantages over stochastic (random) or reductive (simple, linear) systems. Neurons and neuron clusters effectively utilize chaos. One hallmark of chaos is the extreme sensitivity to initial conditions(Bird, 2003). This leads to the classic butterfly effect, where a tiny perturbation in the beginning results in enormous changes down the line. Initial conditions played an significant role in the development of Homo sapiens (Bird, 2003). If we travelled back in time, and changed even the tiniest initial traits, today’s human would appear significantly different.

   Chaotic dynamics may play several roles in migraine pathophysiology. For instance, a tiny initial change in blood flow, such as occurs due to a patent foramen ovale (PFO), could eventually lead to the initiation of a migraine. The complex electrical wiring of the brain involves chaotic dynamics (Korn et al., 2003).

   Chaos, migraine, and evolution are intimately interwoven. This paper outlines some of their connections.

 **CHAOS AND THE NERVOUS SYSTEM**

 Chaos is a math-based subset of non-linear dynamics. Chaos improves the adaptability, efficiency, and versatility of neuronal systems. A number of biological systems are governed somewhat by chaotic dynamics. These systems include the ion flow and electrical activity of the brain, the beating of the heart, blood glucose levels, and glycolysis. Several studies have demonstrated chaos at the cellular level in the brain (Schweighofer, Doya, et al., 2004). By evaluating the flow of ions through the energy barriers of the channel protein, maps reveal the chaotic controls. Algorithms and numerical solutions have been constructed revealing when the transition to chaotic dynamics occurs(Landau, Sompolinsky, 2018). Characteristics of chaotic systems include, most importantly, an exquisite sensitivity to initial conditions. Chaos is deterministic and predictable solely from one point to the next, but not beyond that point. The initial conditions are then reset after each point.

 When compared to reductive or stochastic systems, chaotic systems save energy and are more adaptable. Chaotic dynamics are involved in governing cortical spreading depression (CSD)(Pietrobon, Moskowitz, 2014). Chaos has been demonstrated to play a role in K+, Ca+, and Na+ movements. The flow of ions about the cell has been determined to be a combination of randomness, reductive(linear) movements, and chaotic processes. A small initial change in K+ efflux, or Ca+ influx, will result in a large effect downstream. Clusters of neurons, as well as single neurons, fire in

a variety of patterns. These range from regular oscillating patterns to bursts, and everything in between. Neuronal systems undergo transitions that carry them between diverse states (Vreeswijk, Sompolinsky, 1998). Chaotic dynamics partially govern both individual neurons, as well as groups of neurons.

 **CHAOS AND MIGRAINE**

Tiny CNS perturbations may be brought about by the usual migraine triggers such as weather, stress, or hormonal changes. Through chaotic dynamics this may result in plasma protein extravasation (PPE) and cortical spreading depression, both of which are vital processes in the pathophysiology of migraine(Kernick, 2005). Medications affecting CSD may influence the neuronal membrane through chaotic controls. A small number of patients with patent foramen ovale (PFO) have experienced resolution of their migraines after PFO closure. The usual explanation for the PFO induction of migraine is via microemboli. It is also possible that chaotic dynamics play a role. A small change in blood flow downstream (the heart) may induce a significant change in CNS dynamics upstream.

 Chronic migraine pathophysiology involves wind-up and central sensitization(CS) . These are possibly controlled by chaotic dynamics. Thalamic recruitment involved in expansion of the pain area is likely governed by chaotic dynamics. Thalamic-cortical circuits involve chaotic dynamics. The pathological shift of homeostasis observed in chronic CS, with a loss of brainstem inhibition, may actually reflect a lossof chaotic control(Vreeswijk,et al.,1998). This is similar to the loss of control in the heart, resulting in arrhythmia. The brainstem periaqueductal grey (PAG)—important in migraine—has been shown to be under chaotic control thru P/Q- type Ca+ channels.

 Migraine physiology incorporates a combination of genetic and environmental factors. Trigger factors that affect migraine include stress, weather, and hormonal changes. These may affect the delicate balance between interneuronal nonlinear, reductive, and stochastic dynamics. This may lead to chronic migraine. When a system is forced or stressed, nonlinear dynamics may be affected.

 New onset daily persistent headache(NDPH) may result from a perturbation of neuronal dynamics. Emotional, infectious, or other stresses may influence the delicate balance between nonlinear dynamics and stochastic or reductive dynamics. This could lead to chronic head pain. Calcium and sodium efflux occur with CSD. Potassium and P/Q calcium channels are also involved. This complex system is unlikely to be governed primarily by random or linear kinetics. Chaotic controls have been demonstrated to be involved with these ionic movements(Pietrobon, et al., 2014). Chaotic dynamics could explain some of the properties of CSD. The initiation of CSD may be brought about by a miniscule change in potassium levels. This tiny effect may activate receptors and result in a large change downstream. The result is CSD and oligemia. With the potassium efflux partially under chaotic control, the chaos probably helps to regulate the increased cortical hyperactivity inherent in the brain of some migraineurs.

 The trigeminal nucleus caudalis, vital in migraine pathophysiology, may be activated by a tiny initial stimulus. Through chaotic dynamics, this may result in the release of pro-inflammatory peptides and a release of glutamate. CSD leads to increased plasma protein extravasation. Only chaotic dynamics may explain how this may be possible. The medications that affect CSD (amitriptyline, topiramate, sodium valproate) may influence chaotic dynamics via membrane effects. When nonlinear dynamics are involved, it possibly takes less drug to produce an effect. The periaqueductal gray matter is involved in a number of CNS processes, including migraine. There is evidence that the periaqueductal gray is partially controlled by chaotic dynamics(Schweighofer, et al., 2004).

The loss of chaotic dynamics may lead to a pathological shift of homeostasis. The loss of brainstem inhibitory activity may actually reflect a lessening of chaotic control, eventually leading to a migraine. Similar loss of chaotic dynamics may explain certain arrhythmias and epileptic seizures.

 The primary excitatory neurotransmitter in the brain is glutamate. Along with calcium, glutamate is crucial in the feedback process. Glutamate is directly involved in bi-directional communications between neurons and astrocytes. It is likely that glutamate feedback processes are critical in the generation of complex bursting oscillations in astrocytes. These glutamate-mediated events are involved in migraine, epilepsy, and memory storage. The control of this feedback process may be partially enacted through chaotic dynamics. The cascade of magnesium binding to N-methyl-D-aspartate (NMDA) in the periphery about the brain, with subsequent calcium influx, is very sensitive to minute initial changes(Kernick, 2005). This cascade is important in peripheral sensitization, which leads to migraine attacks. These magnesium and NMDA effects may be under chaotic control.

 Brain-derived neurotrophic factor (BDNF) is a neurotropin that modulates neuronal membrane excitability. BDNF was used in one study to affect hippocampal neurons(Fujisawa, Yamada, Nishiyama, Ikegaya, 2004). Chaotic dynamics partially govern patterns of electrical activity in hippocampal neurons. The hippocampal electrical system is a deterministic one with a few degrees of freedom. Neuronal chaos may be sensitive to change by the application of small amounts of materials, such as BDNF, that influence temporal spiking. The application of BDNF to cultured hippocampal neurons enhanced spike timing and resulted in stereotyped firing patterns. It was felt that BDNF influenced chaos through effects on membrane levels of sodium(Fujisawa, et al., 2004). BDNF enhanced membrane conductance and thus stabilized the membrane. The application of BDNF affected the switching between periodic and aperiodic neuronal oscillations. BDNF has been linked to modulation of neuroplasticity. The BDNF application decreased irregularity of firing patterns by modulating neuronal outputs as well as inputs. The result was a BDNF-induced chaos stabilization. This was the first experiment to demonstrate a pharmacological stabilization of chaos at the neuronal level(Fujisawa, et al., 2004).

 **CHAOS AND EVOLUTION**

 Chaos and evolution are intimately interconnected. There is a chaotic (non-linear) connection between phenotype and genotype. This complex relationship is constantly in flux. A single mutation may be inconsequential, or it may result in enormous changes that are unpredictable. This is typical for a non-linear system. With these unpredictable mutations, iterations over thousands of generations will usually result in evolutionary changes(McKee, 2000). It is debatable as to how much the environment plays a role, versus genetic changes that are generated internally.

 The unpredictability of evolution is typical of non-linear systems. Most discussions of evolution predictors focus on random, stochastic processes (mutations, genetic drift, random environmental changes). A reductive system would behave in a much more orderly, predictable manner. However, these fixed reductive systems are limited, and non-linear dynamics allows for enhanced evolutionary adaptability. The behavior of evolutionary systems is extremely sensitive to initial conditions. This was demonstrated during the quaternary period. At the beginning of each interglacial, the initial circumstances determined the outcome of that period. Between interglacials there were differences that were unpredictable, due to the non-linear nature of the system(Bird, 2003).

 Non-linear dynamics lead to a system that is not scaled. The tree of life is fractal, and follows non-linear dynamics. The branches of the tree are continuously being split, resulting in evolutionary changes. If we travelled back 5 million years, and re-started the human evolutionary process, the result would be dramatically different. This is the nature of a non-linear system. A simpler stochastic reductive system would be predictable but limited. It has been demonstrated that, when many traits interact, chaotic dynamics may govern phenotypic evolution. Ancient species in human evolution, such as Australopithecus and Homo habilis, may have diverged due to chaotic dynamics(McCann, Yodzis, 1994).

 Natural selection utilizes chaotic dynamics, chance, and coincidence(McKee, 2000). Natural selection does not invent, it tends to mosey along and tinker. The chance mutation must be coincidentally beneficial because of some environmental change. For instance, if our ancestors needed robust teeth due to changing climactic conditions, those who happened to have larger teeth would have prevailed. Chaotic dynamics oversees chance and coincidence in the evolutionary process.

 **EVOLUTION AND MIGRAINE**

Examining evolutionary systems in relation to disease is much more than an academic exercise. The evolutionary history will give us a complete picture of a disease. Understanding the evolutionary foundation may help us in developing safe and effective treatments.

 Illness can be considered through two frameworks: 1. a proximate view, and 2. an evolutionary lens. The proximate view considers the nuts and bolts of a disease: pathophysiology, treatment, biochemistry, etc. It’s vitally important to also consider the disease process using an evolutionary viewpoint(Perlman, 2013). One essential question is: “why have migraines persisted, and why are humans still so susceptible to migraine?” The proximate lens says that migraine is a physical trait that involves multiple physiologic systems. The evolutionary framework begs the question: “why does our DNA code for migraine?”

 There are physiological trade-offs that permeate evolution. While sickle cell disease is devastating, the sickle cell gene does also protect against malaria. Cystic fibrosis also involves serious trade-offs. Heterozygotes for cystic fibrosis were less likely to suffer dehydration from illnesses such as cholera. Genes exist to propagate themselves, sometimes to the detriment of the organism (the “selfish gene”)(Dawkins, 2013). This is also the story of migraine. Evolutionary benefits from migraine are possible(Loder, 2002). It is also possible that our species simply continues to be vulnerable to migraine, and the evolutionary benefits are few. There are multiple genes involved in migraine, and evolution does not easily remove “bad genes”(Loder, 2002).

 It’s likely that migraines in humans increased as a result of our migration to more northern latitudes(Vigano, Manica, Di Piero, Leonardi, 2019). Low vitamin D levels may help explain the increase in prevalence of migraine farther north(Prakash, 2010). The TRPM8 gene involves a receptor that plays a part in cold sensation and thermoregulation. TRPM8 (the “T” variation) is also linked to an increased risk for migraine(Dussor, Cao, 2016). People who carry the “T” variation are better adapted to cold environments, and this adaptation likely improved their survival and reproductive success. Migraine may have been a negative consequence from this cold adaptation: another trade-off. The TRPM8 and latitudinal studies were the first to link migraine, evolution, natural selection, and geography(Vigano, et al., 2019).

 The reasons why migraine persists are varied. While there is no epidemiological data from past millenia, the prevalence of migraine may be increasing. An increased sensitivity to light, smells, and sound could be beneficial under certain conditions. Migraine may be advantageous in combating certain infections(Loder, 2002). This may occur through an enhanced immune response, or by an increase in blood flow. Only a small percentage of people never experience headache (7% of men, and 1% of women), signaling that there may be some evolutionary advantage of headache.

 Certain genes that result in harmless “quirks” in one environment can have deadly outcomes in other venues. Our modern environment certainly contributes to migraine frequency. The environment has radically changed, after millions of years of evolution(Cochran, Harpending, 2009). For the vast majority of human history, we were primarily hunting and gathering. Recently, only 10 to 12 thousand years ago, societies in Southwest Asia (the fertile crescent) began to cultivate plants and domesticate animals. Many factors may contribute to increased migraine frequency: changes in culture, living circumstances, agriculture and diet, environmental toxins, densely packed populations, infections (particularly viral), harsh indoor lighting, loud speakers, poor sleep, and increased stress(Loder, 2002). When modern hunter-gatherer societies switch to our “western diet,” they suffer from heart disease and an increase in cancer(Milton, 2000). One of many examples where a changing environment has an impact on disease involves the genes for heart disease. These genes may not have been particularly detrimental for Stone Age humans, due to short lifespans. But as lifespans have been significantly lengthened, these genes have become threatening. Phenotypic and adaptive plasticity are significant factors in humans adapting to the changing environment(Perlman, 2013).

 While migraine is three times more common in women than in men, the evolutionary explanation for this is unclear. Men generally did most of the hunting and gathering, for which migraine could pose disadvantages. For child care, food preparation, and homekeeping, migraine may possibly offer small evolutionary advantages. Migraine commonly decreases during pregnancy, providing an evolutionary incentive for more pregnancies.

 It’s likely that migraine only afflicts the human species. Our ancient human brainstem has obstacles in coping with a cortex that is recently enlarged. With excessive afferent input, our brainstem may be overwhelmed. Having higher cortical functions not found in other primates may contribute to our continued vulnerability to migraine.

 Migraine may function as a defense mechanism against excessive stress, noise, or light(Loder, 2002). The elevated sense of smell may serve as a defense from toxins or viruses entering the CNS. Vomiting may help to remove toxins. Women migraineurs probably have a lower prevalence of type 2 diabetes, compared to those without migraine(Fagherazzi, El Fatouhi, Fournier, et al., 2019). An activation of the trigeminal nuclear complex could be protective(Loder, 2002). If migraine offers protections for an individual, then that individual’s genes may be propagated more successfully. If an ancestral human experienced 100 migraines during a year, and just one of those migraines protected the person from harm, the trade-off would have been worthwhile. In an evolutionary framework, the cost of migraine may be inexpensive.

 There is a difference between a defense and a defect. Coughing is a defense, but becoming blue from hypoxia is not. We want to retain our natural defenses. The calcitonin gene-related peptide (CGRP) associated with migraine may be advantageous under stress(Kee, 2018). CGRP has existed in a variety of species for hundreds of millions of years. CGRP plays various roles in the body, some positive, some harmful(Kee, Kodji, Brain, 2018). Under stress, CGRP is beneficial for our cerebrovascular and cardiovascular systems. Disrupting this natural defense, as happens with our CGRP monoclonal antibodies that prevent migraine, may be harmful. The CGRP story is one example of the danger in ignoring the evolutionary importance of a compound.

 Natural selection is dependent on reproduction. After the reproductive years, a particular trait could very well become detrimental, but that does not affect gene propagation. In order to understand a trait (or disease) such as migraine, we must consider all of the evolutionary processes. These include genetic drift, mutations, migration, non-random mating, and natural selection(Perlman, 2013). Sometimes, natural selection produces opposing effects, resulting in a heightened vulnerability to disease.

 It’s imperative to not only view individuals through an evolutionary lens, but to also consider the phylogeny of the species(Perlman, 2013). The relationships between humans have morphed in the past 12,000 years(Cochran, et al., 2009). One primary factor driving phylogenetic changes is the increase in population density, resulting in most humans living in significantly smaller spaces. Culture, which influences our state of disease or health, may also contribute to an increase in headache prevalence.

 Headache and pain are adaptive responses. Being still, or in bed, may help repair damaged tissues. Incomplete or inadequate natural selection is often cited as the cause for our flaws or disease, but it is more likely that many illnesses are the result of compromises and/or design flaws(Nesse, Williams, 2012). For example, our esophagus crosses our trachea. Because of this, our airway must inconveniently be closed every time that we swallow, to prevent choking. Allergies, atherosclerosis, nearsightedness, and nausea in pregnancy are similar examples stemming from evolutionary compromises and design flaws(Nesse, 2005, 2012).

 Another important evolutionary concept to consider is intrinsic vulnerability(Nesse, 2011). Different species have various levels of vulnerability to certain diseases. Humans mature rather slowly, with infrequent reproduction. This is a factor regarding enhanced vulnerability of our species to certain diseases. It’s difficult for us to rid ourselves of genes that cause harm. Migraine involves a multitude of factors and genes, and it’s not likely that natural selection would be capable of eliminating migraine.

 To more wholly understand migraine, we should venture beyond the proximate and physiologic processes. The evolutionary foundations of migraine are vitally important to study. Examining migraine under an evolutionary lens may help us in evaluating the safety of new treatments, such as the CGRP monoclonal antibodies. We must pay attention to evolution.

 **CONCLUSION**

   Chaos, migraine, and evolution are intertwined. Chaotic dynamics are vital within the central nervous system. Chaos is important at the ionic, neuronal, and neuronal cluster levels. Chaos may be involved in the generation of CSD. Sensitization and wind-up, crucial components of migraine, probably incorporate chaotic dynamics.

   Evolution and natural selection involve chaos, chance, and coincidence. The evolutionary result of thousands of generations depends exquisitely upon initial conditions, characteristic of chaotic dynamics.

   For myriad reasons, our species remains remarkably vulnerable to migraine. To understand migraine, we have to look farther than simple physiologic and proximate processes. We cannot truly understand migraine without examining the evolutionary underpinnings. The safety of new migraine treatments should be evaluated under an evolutionary lens.

 **REFERENCES**

Bird, R. (2003). *Chaos and Life: complexity and order in evolution and thought.* NY,NY: Columbia University Press.

Cochran G, Harpending H (2009). *The 10,000 Year Explosion: How civilization* *accelerated human evolution.* NY,NY: Basic Books.

Dawkins,R. (2016). *The Selfish Gene.* Oxford, UK: Oxford University Press.

Dussor G, Cao,Y-Q. (2016). TRPM8 and migraine*. Headache, 56,* 1406-1417.

Fagherazzi G, El Fatouhi D, Fournier A. (2019). Associations between migraine and type 2 diabetes in women: findings from the E3N cohort study. *JAMA, 76,* 257-263.

Fujisawa S, Yamada M, Nishiyama N, Ikegaya N. (2004). BDNF boosts spike fidelity in chaotic neural oscillations. *Biophysics J, 86,* 1820-1828.

Kee Z, Kodji X, Brain SD. (2018). The role of calcitonin gene related peptide(CGRP) in neurogenic vasodilation and its cardioprotective effects. *Frontiers in Physiology*, 9, 1249.

Kernick D. (2005). Migraine—new perspectives from chaos theory. *Cephalalgia, 25,* 561-566.

Korn H, Faure P. (2003). Is there chaos in the brain? *C.R. Biologies, 326*, 787-840.

Landau ID, Sompolinsky H. (2018). Coherent chaos in a recurrent neural network with structured connectivity. *Computational Biology,* Retrieved May 20, 2020 from <https://doi.org/10.1371/journal.pcbi.1006309>

Loder E. (2002). What is the evolutionary advantage of migraine? *Cephalalgia, 22,* 624-632.

McCann K, Yodzis P. (1994). Non-linear dynamics and population disappearances. *The American Naturalist, 144,* 873-879.

McKee, J (2000). *The Riddled Chain: chance, coincidence, and chaos in human* *evolution.* Piscataway,NJ: Rutgers University Press.

Milton K. (2000). Hunter-gatherer diets: a different perspective. *The American* *Journal of Clinical Nutrition, 71*, 665-667.

Nesse,RM. (2005). Maladaptation and natural selection. *The Quarterly Review of* *Biology, 80,* 62-70.

Nesse,RM. (2011). Ten questions for evolutionary studies of disease vulnerability. *Evolution Applications, 4,* 264-277.

Nesse,RM, Williams GC. (2012). *Why We Get Sick: the new science of Darwinian* *medicine.* New York, New York: Vintage Books.

Perlman R. (2013). *Evolution and Medicine.* Oxford, UK: Oxford University Press.

Pietrobon D, Moskowitz MA. (2014). Chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. *Nature Review Neuroscience,* *15*, 379-393.

Schweighofer N, Doya K, et al. (2004). Chaos may enhance transmission in the inferior olive. *Proceedings of the National Academy of Science, 101*, 4655-4660.

Vigano A, Manica A, Di Piero V, Leonardi M. (2019). Did going north give us migraine? An evolutionary approach on understanding latitudinal differences in migraine epidemiology. *Headache, 59*, 632-634.

Vreeswijk C, Sompolinsky H. (1998). Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science, 274,* 1724-1726.