SYNAPSES, SCHIZOPHRENIA, AND CIVILIZATION: WHAT MADE *HOMO* SAPIENT?

by Lyman A. Page

Abstract. Progress in technology has allowed dynamic research on the development of the human brain that has revolutionized concepts. Particularly, the notions of plasticity, neuronal selection, and the effects of afferent stimuli have entered into thinking about brain development. Here I focus on development from the age of four years to early adulthood, during which a 30 percent reduction in some brain synapses occurs that is out of proportion to changes in neuronal numbers. This corresponds temporally with changes in normal child behavior from the loose-associative, almost schizoid, thinking and art of the four-year-old to the more trained, or disciplined, or acculturated—and restrained—personality of the young adult. I propose that the synaptic changes can best be thought of as a winnowing process likely subject to environmental influences. Acquisition of language and the ability to link linguistic cognition to the plastic development of the brain provide a potentially powerful means of explaining the evolutionally explosive development of human cognition and culture. Schizophrenia, a disease that can be envisioned as representing a derangement of synaptic maturation, may provide an entry into the search for genes controlling the processes mediating the unprecedented development of *Homo sapiens* over the past 40,000 to 70,000 years. The recently completed mapping of the genome of the chimpanzee provides a new frame of reference that may speed the search.

Keywords: autocatalysis; brain development; cognition; culture; emergence; evolution; genetics of brain function; human brain; plasticity; puberty; religion; schizophrenia; synapses

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A major source of concern among those who ponder evolution is the challenge of explaining development of the human brain, and more particularly the mind, from purely natural causes. One of the stalwarts of the molecular biology revolution even posited that the human brain might be incapable of understanding itself (Stent 1968), a kind of biological uncertainty principle. Since then, enormous advances have occurred both in molecular biology and in the study of the biology and development of the brain. A sizeable number of genes involved in cognition and others involved in regulating the dynamics of brain structure (especially synapses) have already been identified, at least tentatively. In some ways the complexity of the advancing knowledge makes it paradoxically easier to devise concepts of what our brains are doing and how consciousness could have come about. Ideas of complexity (Waldrop 1992) and emergence (Goodenough and Deacon 2003) have provided stepping stones to conceptual understanding of how brain biology can lead to what we call the mind and thence to civilization, religion, arts, and sciences—in short, culture.

Herein I outline a simplistic, inherently intelligible, testable scenario consistent with current biological knowledge by which the extraordinary development of human cognition and the mental activity that accompanies it might have evolved in an autocatalytic way that compressed it into an eye-blink of evolutionary time. I pretend for simplification that a crucial step was a single process, although that seems unlikely. The scenario uses a classical molecular biological paradigm,[1] but one must recognize that evolving understanding of the role of "non-gene" RNA in the complexity of regulation of cellular function will open new vistas (Mattick 2005; Claverie 2005).[2]

The idea of environmental effects on brain function in animals goes back to the early twentieth century and gradually has been extended to humans. By the 1970s anatomical effects of experience on the development of the communicating connections between brain neurons—the synapses—had been demonstrated in rats (Rozenzweig, Bennett, and Diamond 1972). Regionally selective synaptic reduction (Huttenlocher and Dabholkar 1997), white matter (axonal) changes (Paus et al. 1999), and variations in the gray matter of the cortical mantle (Shaw et al. 2006) are a regular part of normal postnatal human brain development. The relevance of this concept to aspects of evolution and disease will be discussed further.

A Selective Recent History of *Homo*

The hominid ancestral line split away from our closest relatives, the chimpanzees and bonobos, about 5–6 million years ago (Dawkins 2004). The chimpanzee genome sequence has recently been determined, allowing a comparison between our species and theirs of protein-coding sequences and gene activities. Such a study, using brain, heart, liver, kidney, and testis, shows that both structural changes in genes and expression of genes

in the brain and testis show excess differences over such changes in other tissues and suggests that these reflect crucial evolutionary events involving cognition and male reproduction (Khaitovich et al. 2005).

The focus of this essay is our species' "Great Leap Forward" (Diamond 1999), so this "history" focuses on the millennia surrounding that "event," with special emphasis on cultural aspects, particularly language and its consequences, religion, philosophy and mathematics, arts and sciences. It appears that this phase of human development occurred in more or less parallel fashion in Europe, the Far East (Diamond 1999, 218–19; Bodde 1948), and the Americas (Saturno, Stuart, and Beltran 2006; Houston 2006). I focus on Europe, where data are more plentiful. The narratives provided by Jared Diamond (1999) and Richard Dawkins (2004) provide readable summaries and entries into the vast and evolving literature on which they are based.

Somewhere around 100,000 years ago *Homo sapiens* in the form of Cro-Magnon man appeared out of Africa in the Middle East, where *Homo neanderthalis* was indigenous and had already spread to Europe. Neanderthals buried their dead, suggesting that their culture included religious ideas, but had relatively crude use of tools compared to Cro-Magnons. Between 50,000 and 40,000 years ago *Homo sapiens* was in Europe, and by 28,000 years ago *Neanderthalis* was gone. There is no evidence of war or interbreeding, so the current view is that Neanderthals were just "replaced" (Klein 2003), apparently by losing the competition for resources. They had skulls larger than those of Cro-Magnons, wider but shorter, and with sloping foreheads that would seem to allow less space for frontal and prefrontal regions of the brain. These regions are considered critical to uniquely human cognitive functions, including emotional, aesthetic, and executive (decision-making, planning, prioritizing) activities and are involved in the circuitry used for the vast array of human activities that require these functions (Miyashita 2004).[3]

Between 100,000 and 40,000 years ago the tools used by Cro-Magnons became vastly more complex and standardized than the crude stones of their forebears and included shaped tools, multiple-piece tools, thrown weapons, and sewing and fishing materials. From that period the pace of human development quickened. By 20,000 years ago cave art was well underway. It is difficult not to believe that the artists of the caves also had complex communication—language—and that human lore, including religion along with the art, was established. Agriculture and domestication of animals appeared around 10,000 years ago in the Fertile Crescent (and probably later in India). About 5,000 years ago logographic writing appeared in Sumeria and Egypt. In the West, alphabetic (narrative) writing condensed from the misty Homeric tales 2,700–3,000 years ago, and Plato wrote a few centuries later. In that time what seems (to me) rather crudely simple philosophy in Homer evolved to Socratic and Sophoclean subtlety.[4]

If this timeline seems to represent exponential progression of knowledge and complexity of thought, it is meant to. Moreover, in Western Europe, with a slight hiccup after the fall of the Roman Empire, it continues to be so. My grandfather, who picked me up on the day of my birth, was born in 1846. The changes in human history and thought in the span of our two touching lives can be said to exceed the changes of the preceding two millennia. In the area of biology, for example, the works of Louis Pasteur, Gregor Mendel, and Charles Darwin appeared in this interval, and molecular biology opened the black box of the cell. Exponential rates of change suggest autocatalysis. The logical suspects for bringing about autocatalytic human change are cognition and acculturation.

A Moment in Evolution

Let us imagine that we can look at metabolic packages in the brain of a three- to four-year-old Cro-Magnon (*Homo sapiens*) some 5.9 million years after the ancestral line separated from that of the bonobos and chimpanzees (Dawkins 2004, 100ff., 455). We can look at tapes (or, in these days of complexity, DVDs) that carry the information of metabolic pathways of different cells or cell types. For example, we can look at the way a class of neurons uses the energy available to it to regulate the processes by which the neuron's axons and dendrites—its sending and receiving tentacles—grow and connect with other neurons, specifically with neurons in the frontal and prefrontal cortical regions, through synapses. I accept the notion that synapses are the crucial element of the brain's cognitive capacity, that complex external information resides not in individual cells of the brain but in the remarkably complex and dynamic—and extraordinarily large—webs of cells connected by these signaling pathways (Summerfield et al. 2006; Suzuki 2006). If we have 100 billion neurons, and each can have up to 10,000 synapses with other neurons that mediate cell-cell communication (Changeux and Ricoeur 2000, 78), and these synapses can be turned off and on in all combinations and permutations, the number of possible brain states is enormous.[5] The capacity of the human brain is an emergent result of these networks (Goodenough and Deacon 2003).

We know that in our child there is already a substantial network of these connections because this brain has been growing since very soon after conception, as have the brains of our chimpanzee cousins. The Cro-Magnon brains, however, are triple the size of the chimpanzees', most of the extra size being acquired after birth. These processes are very well established in response to genetically dictated programs ("hard wiring") probably modified by the conditions in which the growth occurs as mentioned previously. We know also that in the human brain there exists the product of a gene, FOXP2, that appears necessary for complex language use, with human-specific mutations from the homologous gene in our chimpanzee

cousins fixed within the last 200,000 years (Enard et al. 2002). This almost surely means that there is verbal communication between individuals. Doubtless, when an adult demonstrates some technique to a child, the demonstration includes verbal elaboration, which is included at some level in the child's memory of the demonstration. This is already an elaboration of the tool-based cultural transmission in chimpanzees (Whiten, Horner, and De Waal 2005).

As we look at the tape of these neuronal processes in our selected child and compare it with her grandfather's we see a new protein in this class of neurons, a complex protein that looks as if it's in a transmembrane signal-transducing receptor family of proteins.[6] It turns out that this receptor/transmitter receives signals from the audiovisual/language neuronal complex and transmits them to the synapse-regulating machinery of the cell! Thus, this new gene connects an important perceptual-language part of the cognitive apparatus to the complex apparatus regulating the formation of synapses between neurons in the executive (frontal and prefrontal) region of the brain. This connection profoundly changes the direction of the developing structure and connectivity—hence function—of the brain by adding linguistically cognitive information, including the abstract—stories, religion, folklore—to the influences on continuing brain development. Her neuronal connections are being streamlined, directed efficiently to handle the cultural and intellectual world into which she was born. Her assimilation of cultural information is thus embedded in her brain in a way unmatched among her peers (who of course are therefore no longer "peers"), and her brain has been physically oriented to process the information as if it had long been bathed in that very cultural tradition. This adds lingual and cognitive culture as a component of any other memory she acquires and of her decisions and planning, a *quantum* leap from the tool-related "culture" attributed to the chimpanzee (Whiten, Horner and De Waal 2005). This occurrence ranks as an evolutional "Good Trick" (Dennett 1995, 77). Her communication to her family, friends, and future children will virtually unconsciously incorporate her clan's cultural traditions as well as new learning. Her children who share this genetic endowment will have similarly enriched plastic brain development that is additionally enhanced by the new learning and elaborations acquired by our child as she matures.

Thus, each generation starts from a new baseline that incorporates the old. Her communication and that of her children will enrich their social relations, particularly with those who can appreciate the value of the enrichment. The result in time will be sexual selection for this trait.[7]

Selection for favorable characteristics, in contrast to Darwin's concept of the pace of evolution, can be very fast (Mayr 2001, 117–18), as, for example, in the selection of antibiotic resistance among bacterial populations.[8] In humans, in populations living where malaria was endemic, the

widespread entrenchment of the sickle-cell gene, which in the heterozygous state confers resistance to malaria, is estimated to have occurred in one hundred generations, or about two thousand years (Mayr 2001, 196). The postulated Good Trick "event" described above is at a time in human history when our species was recovering from a severe population bottleneck brought on by a prolonged ice age (Dawkins 2004, 405) resulting in a small and relatively genetically uniform population. This population state also allows for more rapid evolutionary change, and it makes the appearance of beneficial mutations more likely (Mayr 2001, 137). Thus, conditions were good for sexual selection and rapid fixation in the population of the gene for this new favorable trait.

Schizophrenia Viewed as Aberrant Synaptic Pruning

Where would one start to look for genes that could have such an effect on human development? Nearly one hundred years ago Sir Archibald Garrod ([1909] 1963) recognized that "experiments of nature"—his term for genetic diseases caused by mutations—could give insight into normal metabolism. In those days it was the abnormal enzymes that revealed the importance of the normal ones. The concept now is routinely applied to genetic studies. For purposes of argument, therefore, I suggest considering schizophrenia as an experiment of nature that may open a door to understanding recent evolution of cognition. If one can identify genes that underlie this disease, one of them may be a mutant allele of an evolutionally important brain-organizing gene. The same idea is being applied in studies of genes involved in microcephaly (Evans et al. 2005; Mekel-Bobrov et al. 2005) and bilateral frontoparietal polymicrogyria (Piao et al. 2004).

Symptoms of schizophrenia include loose association of ideas, hallucinations, delusions, confabulation, and other characteristics that can be said to be present in normal four-year-old children (Tsai and Champine 2004, 389). Such children's conversations may include experimental word groupings and scraps from widely divergent sources. The children may have imaginary friends with whom they converse; they happily invent all sorts of fabulous experiences; and their art is experimental and ungoverned initially by rules (Gaitskell, Hurwitz, and Day 1982, 144; Slade and Lieberman 1997, 95–96).[9] All of this changes by the time they are twenty-two, by which time most of their synaptic winnowing has occurred.

It is tempting to view schizophrenia as an aberrance in the winnowing process. It is not a new idea (Feinberg 1982; Lewis and Levitt 2002; Cowan, Harter, and Kandel 2000). There are anatomical findings in schizophrenia and changes from the normal on imaging and by clinical studies that might be attributable to altered pruning of synapses (Cowan, Harter, and Kandel 2000, 379–80), and the disease typically becomes manifest late in the second or in the third decade of life. There is thus mounting support

for the idea that schizophrenia results from disordered neurodevelopment (Lewis and Levitt 2002). Deficient pruning, excessive pruning, or deranged pruning are the obvious possibilities, any of which could be the result of altered gene(s). That schizophrenia usually if not always involves a genetic component has long been accepted on the basis of twin studies (Kety et al. 1971), but those same studies also imply that there is a nongenetic component.[10] Therefore, as in many other strongly genetic diseases (such as multiple sclerosis and type I diabetes mellitus), one thinks of genetic *susceptibility* to the disease rather than strict inheritance. Nongenetic, or environmental, factors were long suspected even to be primary in the causation of schizophrenia, and the discussion above makes clear that such factors are involved in the process of synaptic development, but none has yet been shown to be specifically associated with schizophrenia.

Two of the candidate genes already proposed as causing susceptibility to schizophrenia, *Epsin 4* (Pimm et al. 2005) and *Synapsin II* (Chen et al. 2004), are involved in synaptic regulation. Another candidate gene, NRG 1, which is associated with schizophrenia in Iceland, has a role in the expression and activation of synaptic neurotransmitter receptors. It has been experimentally mutated to provide a behavioral mouse model (Stefansson et al. 2002). Studies in other countries, however, failed to support this gene's association with schizophrenia. The problem of finding a general gene for susceptibility to schizophrenia is complicated by the complexity of the disease, the likely frequent involvement of multiple alleles (Cowan et al. 2000, 374), and the existence of subtypes (Hallmeyer et al. 2005). Nonetheless, as data more firmly establish a relationship between genes and susceptibility to schizophrenia, it would seem potentially fruitful to explore the histories of suspected genes along the lines that Wolfgang Enard and colleagues (2002) have done for FOXP2, comparing them with the chimpanzee for potential roles in the development of human cognition.

Discussion

The scenario outlined above is only a single thought of many on crucial developmental changes in the evolution of the human brain (see Piao et al. 2004; Evans et al. 2005; Mekel-Bobrov et al. 2005). Indeed, the reports by Patrick Evans and Nitzan Mekel-Bobrov and their colleagues present evidence of strong selection of brain-relevant genes during the era of interest—mutations selected since 37,000 and 5,800 years ago, respectively. This latter event even tampers with the dearly held notion that all mutations in the human genome that could occur have already occurred (Rakic 2004). I have selected synaptic development because its very existence seems to serve as a "topping up" of a well-developed brain whose earlier cognitive base would not have allowed the Great Leap Forward. Hence, our species' prolonged prepuberty and adolescence allow us to get four-year-olds jiggered (fortunately, never completely) before they start to run

the world.[11] The obvious result is that thinking in a new generation is based on assimilated knowledge and culture to which are added new ideas, a substrate for change that could be predicted to occur progressively rapidly (exponentially increase) with each new generation and increasing complexity of the cultural substrate. This is a state of plasticity such that environmentally driven epigenetic brain development is an established, continuing, autocatalytic event.

The occurrence of a genetic disease, schizophrenia, that may involve derangement of synaptic pruning provides an investigative focus that makes the idea seem additionally attractive, especially because this disease represents a subtle derangement of the impressive complexity of the brain. The subtlety is well shown by Sylvia Nasar in her book *A Beautiful Mind* (1998) and especially in the film based on it, in which the director masterfully draws the viewers into John Nash's delusional world. In addition to subtlety, schizophrenia's effect seems to be particularly prominent in the prefrontal region of the brain, both clinically and by imaging studies (Cowan et al. 2000, 378–79). As the executive area of brain function, this is just the region one would select to look for changes that suddenly made the human brain so effective that the species rapidly became dominant. One thinks of cultural development and intergenerational transmission of information as critical features of this dominance (Burhoe [1988] 2006), and these are, again, capacities in which prefrontal participation is thought to be crucial (Miyashita 2004). It is my presumption, and I think that of Ralph Burhoe ([1981] 2006), that religion (and philosophy), art, spoken lore, and science all developed in tandem when the brain's capacity for them arose. Diamond (1999, 39ff.) has pegged the Great Leap Forward at between 100,000 and 50,000 years ago. Jewelry dates from about 40,000 years ago, and certainly by 20,000 years ago skilled cave art, sculpture, and complex tools, which required experimentation to develop, are entrenched. Religion and all of the complex cultural accomplishments that go with it had to have been well entrenched also. Thus, one looks for genes (or regulatory RNAs) that mutated to the modern sequence before those times. How long before could be a measure of how important a single mutation might have been. In any case, it no longer seems an impossible dream to understand what has happened and is presumably happening to *Homo sapiens*' brain.

NOTES

1. By "classical molecular biology paradigm" I mean the "central dogma" of information transmission from gene DNA to messenger RNA to protein (especially enzymes) that developed in the early years after the elucidation of the structure and probable function of DNA (Watson and Crick 1953) and the various modifications, such as mRNA splicing, that have occurred since.
2. The issue of *Science* in which these articles appear includes seven papers and an editorial on this important subject. As we should have suspected, it certainly looks as if evolution has not, after all, wasted all of those high-energy polynucleotide bonds making junk DNA. The welter of so-called noncoding RNAs can be expected to provide a huge increase in the understanding of the regulatory armamentarium of the cell as well as to shed light on speculations of the "RNA world" of early life (Riddihough 2005). It also means that we should think carefully about statements referring to the number of "genes" in genomes, since the noncoding RNA doubtless has many functions of the same types of importance that we traditionally have thought of as related to classical gene products. For example, human microRNA from a noncoding DNA segment recently has been implicated in the regulation of a gene implicated in the Tourette syndrome (Abelson et al. 2005). In the twenty-one months since this paper was written, the number of biologically active noncoding RNAs has increased to "several thousand" (Pennisi 2007).
3. Neanderthals also had a unique structure of the labyrinth of the inner ear, critical to balance and spatial orientation. Whether this had anything to do with their extinction is an intriguing question.
4. Alfred North Whitehead famously commented that his life's work was a footnote to Plato.
5. The number the cited authors used for synapses is 10^{15}. If all permutations are possible, the number (factorial) of brain states would be about 5×10^{29}. In reality, there are probably physical constraints on the number of permutations, so this is a top estimate. The number of brain states is still very large, made larger by ongoing repatterning of individual synaptic responses, judging from animal studies (Abbott, Varela, and Nelson 1997; Callaway 2006; Cheung et al. 2006; Cook et al. 2006).
6. These "families" result from duplication and modification of already existing genes. From the type of structure of the protein deduced from amino-acid sequence or genetic-code sequence data, one can guess at the probable type of function of a newly discovered gene product. Gene duplication occurred to a colleague and me in the course of writing a paper on a different but related topic (Englander and Page 1965). It was to us a new idea, and I still do not know if there exist earlier discussions of it. It was immediately obvious that it represented a powerful evolutionary tool, so we put it into our paper. It was one of those epiphanic moments that make the concept of religious naturalism real (Goodenough 2003).
7. In discussions of the "Baldwin effect" Daniel Dennett (1995, 77–80) and Ernst Mayr (2001, 200, 284) seem rather vague, describing the effect as mediated by "favoring" by natural selection of a "Good Trick," but Dawkins (2004, 72) relates it to sexual selection.
8. An organism adapted to a stable environment will grow in population and exhibit slow genetic change, because the vast majority of mutations will be deleterious and will be weeded out. This gives rise to Stephen Jay Gould's "punctuated equilibrium" (Dennett 1995, 282ff.). The rare favorable mutation will be selected *for* to a degree depending on its importance to reproduction, either by subtle action of a collection of factors as described also by Dennett as the Baldwin effect (pp. 77–80) or, if it becomes evident in cognitive species or is sexually appealing, by sexual selection. Either of these will induce faster change than those in the equilibrium situation, and sexual selection may be very rapid. If the environment changes in ways important to fitness, as in addition of antibiotic to a bacterial culture, change *must* be fast, sometimes so fast that if the organism does not already have in its polymorphisms alternative means of meeting the new environmental challenge, the species may succumb.
9. The selected features analogized to schizophrenia represent my slant for purposes of this discussion. It is not easy to find in developmental psychology texts pure descriptions of child stages as deviant from maturity, because almost all texts are oriented toward what the child has still to master or is mastering, or what is abnormal, so one reads between the lines. The interpretations agree with those derived from observations over forty-five years of pediatrics and

from the Dr. Seuss books. The purpose here is to emphasize the subtlety of the derangement that we call schizophrenia.

10. In truth, low concordance for a disease among identical twins—for example, 50 percent as in schizophrenia (Cowan et al. 2000)—does not prove environmental involvement in causation, because the mitochondrial genes of identical twins are not necessarily identical. If the product of the mutated gene had to interact with the product of a mitochondrial gene with multiple normal alleles, the mutation would likely have limited penetrance, since it might malfunction only with respect to one of those alleles. Thus, the appearance of disease would depend on the allelic distribution of the mitochondrial gene product involved, not on an environmental trigger.

11. The delay of puberty stems from before our separation from the chimps, whose puberty is a year or two earlier than ours and more delayed after birth than any other primate (Plant 1988). Interestingly, at least some dinosaurs had late puberty (Erickson et al. 2004).

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