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Origin of the Brain

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When I was first invited to talk to you on some subject related to the Origin of the Brain I was appalled, because I am neither an expert in evolution, nor in neuroanatomy, nor in neurodevelopment. Although I do work to some extent in anatomy and in development, the work is confined to a small part of the mammalian brain: for much of the rest I am almost as ignorant as the astronomers in this audience.

But lest those who invited me appear too far mistaken in their choice, let me say that when it comes to the ultimate origin of the brain – the question of exactly what it came from, what forces molded it, and, in detail, how it got the way it is, I think all of us are in a profound state of ignorance. All I or any other neurobiologist can do is to make a few very general statements, which will be almost truisms; one can also point out what some of the major puzzles are.

In considering the origins of something like our own brain, one has three main ways of going about the problem. One can approach it head-on and examine the fossil record, to ask what the brains of our ancestors looked like. When it comes to the nervous system all fossils can do is indicate the bony housing of the brain or spinal cord. While we all sense the far reaching nature of the deductions that paleontologists can make from a single bicuspid tooth about events that occurred over millions of years of history, most people will agree that the insides of skulls are rather limited in the kinds of things they can tell us about the development of an incredibly complex structure like the brain. It is as though some future archeologists were to try to trace the development of computers having only some fragments of the outer box containing them. Of course some valuable hints could be inferred just from the outer box, such as the spectacular decline in size of a computer, and hence the decreasing size of the elements of which it was composed. Perhaps the increasing occurrence of computers in the bedrooms of family dwellings will indicate, among other things, the spectacular decrease in their price.

The second tool for tracing the origin of the brain is comparison with brains of simpler contemporary species of animals. This assumes that there are plenty of animals around today that at least to some extent resemble our ancestors, an assumption that has all of evolutionary theory to back it up. It is an obvious tool, and a powerful one. Third, and finally, there is the well-known fact that the development of an animal to some extent recapitulates evolution – in the case of neurobiology, that the development of the brain in the embryo of an animal can give useful hints about the way in which that brain evolved.

Two hundred years ago one would have to add a fourth source of information, the Bible. The whole question of the origin of the brain is ignored in Genesis Chapter 1, which sadly for my status at this meeting surely does deal with the origin of almost everything else. All botany is taken care of in one or two verses, similarly for zoology; two verses are devoted to man, and curiously almost as many to women.

In order even to begin a discussion of brain origins I feel I should say a few words about nervous systems. It is relatively easy to draw a schematic diagram of a very general brain or nervous system (figure 1). This is to give the astronomers in the audience a rough idea of what kind of thing the brain is. Strictly speaking, the nervous system includes brain and any other aggregates of nerve cells, such as spinal cord and other clumps of nerve cells that are scattered here and there in the body. I will often use the word brain when I really mean 'nervous system'. In the very final analysis the brain can be regarded as

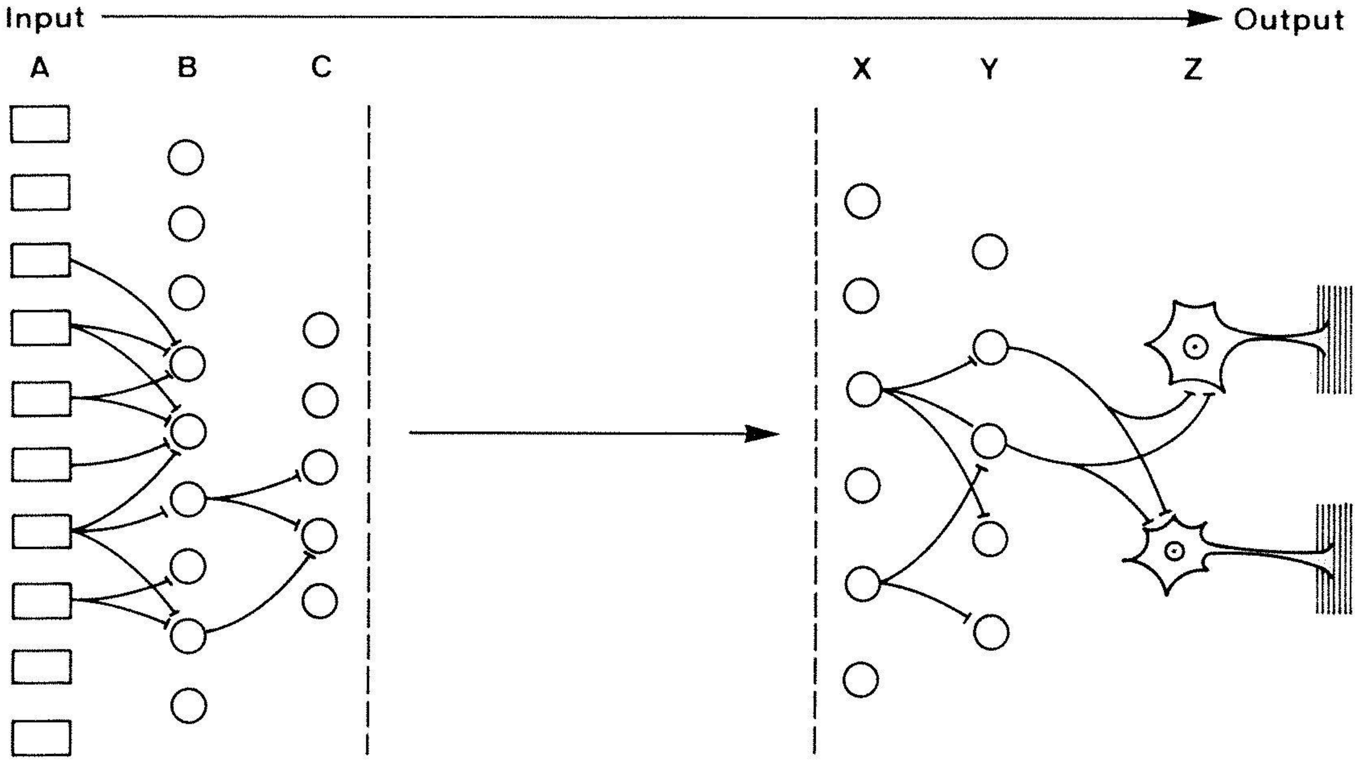

Fig. 1. Overall organization of the brain is indicated in a rough caricature that suggests the flow of information from the input of sensory signals by receptor cells (A) to the eventual output by motor neurons (Z) terminating on muscle cells. The outputs of receptors and neurons usually branch to send diverging signals to the next stage. Most neurons receive converging inputs, both excitatory and inhibitory, from earlier stages. Something is known about the significance of the connections near the input end of the brain (B, C) and near the output end (X, Y). Far less is known about the working of regions in between, which make up most of the brain.

forming a link between the outside world and an animal's muscle cells or gland cells. On the left of the diagram we have cells specialized to take in information from the outside world – information in the form of light (vision), mechanical energy (touch, hearing), and chemicals (smell, taste) – and on the right end, cells that can react in some way so as to allow us to manipulate the outside world. The brain, between these two, can be incredibly complex and many storied, or it can consist, as it does in the simplest animals, of one set of direct connections between input and output. In the most complicated of brains it is both at once. When we see a face, recognize it and smile or grimace, the circuit (path) involved in conveying the messages from the eyes to face muscles is so complex that beyond a certain stage we lose all trace of it. Between the rods and cones in the eye and the muscles of the face must be circuits that allow us to compare the face with others we remember and to recall previous experiences with that particular face, and circuits that have to do with emotion, delight or anger, and finally circuits that make just the appropriate sets of muscles contract together to produce the smile or scowl. No one has any clear idea how many sets of nerve cells are interposed between input and output. A wild guess would be 50–100, but almost certainly there is no single number, but many parallel pathways of varying lengths.

At the other extreme we have the simplest reflexes, very short paths with one or two connections. An example is the knee jerk, in which tapping the knee extensor tendon produces contraction of the thigh muscle. Here only two connections are involved, one in the spinal cord and one at the muscle itself.

The simplest animals have only rather direct paths between input and output. An example would be a worm which responds to poking it in the side by bending away, for example by contracting muscles on the opposite side. This takes a not entirely trivial set of connections going from the skin on the right side to the muscles that run fore-and-aft in the worm on the left, and of course a similar set of connections linking skin on left with muscle on right.

Another primitive example would involve pressure on the inside of the intestine wall, produced by food, leading to constriction of circular muscle so as to propel the food along.

For circuits even as simple as these, animals need to have evolved a special bizarre kind of cell specialized for conveying information – the nerve cell, with its more or less round cell body and long cylindrical or tapering branches that convey electrical signals. Prior to the invention of nervous systems, long-range signalling in the organism had to be done chemically by an endocrine system. In the endocrine system a cell when stimulated releases a chemical that is discharged into the circulating fluid, into the blood stream, for example; when molecules of the chemical reach a sensitive target cell, they interact with some complex molecule on the surface of that cell's membrane, in a specific way, reminiscent of a key fitting a lock, and the union in some complicated way leads to the cell's responding appropriately, by changing shape, growing, releasing some other chemical, or some other change. A certain amount of specificity can be obtained in such a system by making use of dozens or hundreds of different chemicals and the same number of kinds of target receptor molecules. Such a system, in which a chemical is released by one set of cells, diffuses out through the entire animal and influences some matching set of target cells, is simply not refined enough to look after problems such as swimming or locomotion or feeding in a large multicellular animal. It lacks speed and specificity.

The nervous system was quite possibly derived from this endocrine system. We think so because nerve cells and endocrine cells are similar in many respects. At the point where two nerve cells communicate, called the synapse, an electrical signal arriving at the terminal of the first cell causes the release of a chemical, which diffuses out and in less than 1 msec arrives at the closely apposed membrane of the second cell. The result is to produce contraction if the second cell is a muscle, or the release of a second chemical, if the cell is a gland cell, or the production of a second 'postsynaptic' electrical nerve signal if the second cell is a nerve cell. What the endocrine system and the nervous systems have in common is the release from one cell of a chemical that interacts specifically with molecules of a second chemical on the recipient cell, the 'receptor molecules'. The first diffusing molecule, called a hormone in endocrinology and a neurotransmitter in the case of the nervous system, is usually small; several aminoacids are transmitters. The recipient molecule is large and complex, generally a protein. The two systems also have in common an elaborate chemical machinery for release of the first substance, and an elaborate machinery in which the change brought about by the combination or the union of the first substance with the receptor molecule is finally translated into a response – a nerve impulse, contraction, or whatever. Some of the same compounds, such as adrenalin, may occur in the two systems, as the endocrine in the one and the transmitter substance in the second. Many of the details of the release and translation processes are identical in the endocrine and nervous systems and involve substances like cyclic AMP and calcium ions, and multiple phosphorylation steps. The similarity of the two systems is a powerful reason for concluding that one was derived from the other. The advantages of the nervous system are, of course, speed and the possibility of extreme complexity and specificity.

I now want to make a completely different kind of statement about the brain, a statement that would be obvious and a truism to any zoologist in the audience, but which for a non-zoologist is probably worth enunciating. The brain of any animal is not so much a general device for computation as it is a set of devices to solve or take care of a large number of very special problems, often very mundane ones that may give us no very great aethetic satisfaction to contemplate. Take the example of vomiting. We eat a poison, say a liter of schnaps. Now just imagine the intricacy of what happens and the intricate specific circuits that must be called into play in a particular part of our brain, a subdivision called the medulla oblongata. The stomach wall is irritated; signals pass along one set of nerves to the brain; as a result the stomach contracts, the diaphragm and abdominal muscles contract, the pharynx opens, the epiglotis closes (so bile and alcohol don't enter our lungs and give us pneumonia), respiration stops, we sweat. We are likely to feel some emotion, probably not elation. All very elaborate, and not something we learn from our parents or at school. The circuit is there at birth and gets there because of genetic instructions. We have hundreds of such circuits: coughing, sneezing, laughing, crying, blinking, defecating, urinating, copulating, sleeping and moving around while we sleep, walking, running, pulling away from something painful, turning head and eyes when we see or hear something new or interesting, following objects with our gaze, grasping objects placed in the hand, holding and keeping our bodies erect, phonating, yelling, singing, speaking – the list goes on and on, and is of course different for different animals – we don't warble like birds though some of us may yodel, we don't preen our fur or swim like leeches. The point is that we can never understand the specifics of how brains are connected without a knowledge of the organism's behavioral repertoires. Our various little rituals are very particular and mundane, but we have to think about them if we are to understand why our brain is hooked up the way it is. Mathematicians and physicists love generality and all-inclusive ideas, and I think that that is why they sometimes don't get very far in thinking about the brain, an organ that evolved to start with as something to take care of a host of small and special, but for survival very important problems.

Of course, I hardly need say that most of the more complicated problems arise in the part of the body where the sensory organs are placed, where food is taken in, and for most animals except man, the part that leads during locomotion, namely the front end or head. That is the part that requires the most control machinery and that is why the front part of the nervous system becomes larger than any other part, and is consequently dignified by a special term: Brain. Now I have already consumed 25 of my 50 minutes and have barely introduced the subject. From here on I have to be selective and will just touch on a few very diverse questions relating to how our brain got there and why it is designed as it is.

One thing we might wish to consider is the degree to which brains are similar or dissimilar in different animal species. In one respect the nervous system is similar to most other systems in zoology: the brains of invertebrates all have much in common, and are wildly different from brains of vertebrates, all of which likewise have very much, even more, in common. Invertebrate brains tend to be distributed in the form of aggregates of relatively small numbers of cells, called ganglia. A worm or leech has dozens of ganglia, each containing hundreds of cells (not millions), one for each body segment and a larger one for the head. The numbers of cells involved may be small by vertebrate standards but the number of branches or processes of each cell, and their intricacy of interconnections, may be formidable. Invertebrate brains are not at all simple. Invertebrate ganglia generally have one property that our brains utterly lack, something we may term 'cell identifiability'. In a particular lobster abdominal ganglion we can speak of cell No. 321 in two different animals, and know we are talking about the same cell, with almost identical connections and functions; for example, a cell whose firing leads to extending the terminal part of a walking leg of the lobster. In a vertebrate one can almost never speak of a certain particular cell, the way one can of a tooth or a limb or a bone, any more than one can speak of a particular hair on someone's head. For doing research on brains identifiability can be very useful.

Sydney Brenner some years ago began a project whose aim was to take a relatively simple invertebrate, a worm less than 1 mm long and having only the order of 1000 nerve cells, all identifiable (in the technical sense mentioned above) and work out, using the electron microscope, a wiring diagram of all the connections. This is feasible, but it took many years just to get 10% of the way through this humble animal. My point is that 'simplicity' is relative: even the simplest of invertebrates can be incredibly complex. An animal as far evolved as a fly is not simple by any standards.

When most of us think of a brain we of course think of our own, or ours plus our cat's, and not that of a tapeworm or a fly. In the case of vertebrates – such as fish, birds, reptiles, amphibia, mammals, the thing I have always found most unexpected is the similarity of design of the nervous system. Most of the basic parts, or substructures or subdivisions, such as cerebellum, spinal cord, medulla oblongata, occur in all vertebrates; and nothing like any of these occurs in any invertebrate. Vertebrate brains differ in details and emphasis, but all have the same basic plan. The origin of brains like ours is thus tied up very much with the origin of vertebrates from some invertebrate ancestor – a problem on which I can speak with absolutely no knowledge or authority, except to give my vague impression that evolutionists really don't know very much about the origins of vertebrates. It does seem likely that our invertebrate ancestor was much more like a worm than like a clam, fly or lobster. It was what the author of Genesis would have called a 'creeping thing'.

The subject, the origin of the brain, is closely related to the problem of how any given brain originates – the problem of the development of the nervous system. This is a branch of embryology, a vast subject in which much is known, and much still unknown. Here I would like to discuss two aspects of neurodevelopment that particularly interest me.

The first is the distinction between the development of the brain before birth (here I am thinking of mammals) and the development after birth. Prior to birth most or all development must obviously be dictated, ultimately, by genetic information. After birth, the development of connections in the brain obviously has the possibility of being influenced both by genetic and by environmental process, and this is what constitutes learning, in the very broadest sense. The brain of higher organisms, to develop in a normal way to maturity, must be in a normal environment postnatally during a period of flexibility usually termed the 'critical period'. One good example of a critical period occurs in the visual system. If an adult of 65 years develops cataracts, he may become blind for some years, but on removal of the cataracts he will almost invariably see perfectly well provided glasses are fitted to replace the lens of the eye. In contrast, if a newborn baby has cataracts that are removed only say at age 5, vision will at first be totally absent. It develops only slowly and imperfectly. The cause of this blindness is not in the eye, but in the visual part of the cerebral cortex, to which the eye connects. Whether the disuse leads to a withering of connections that were there at birth, or prevents a flowering of connections whose specific details depend on experience, is the question of nature vs. nurture, at present a vexed subject. Most modern neurophysiologists would probably agree that the amount of precoded information in the brain has been seriously underestimated by psychologists of the past century. On the other hand we all agree that the proportion of information contained in the mature brain of a human that got there by postnatal learning as opposed to prewiring is far higher than in any other animal. This may be somehow related to the greatly increased size of the cerebral cortex of man, a subject that I will come back to. It is probably related to the long period in infancy during which a human is completely dependent on its parent. 'Critical periods' tend to be very long in humans, up to 5–10 years in some systems, as opposed to a few months in a kitten and one year or less in a monkey.

No one can look at the hydraulic engineering accomplishments of a family of beavers without being greatly impressed. I doubt that anyone would seriously try to maintain that their abilities came about through attending lectures at 10 o'clock every morning. Just how the civil engineer accomplishes the same thing – and much more – by attending lectures, is the subject of memory and learning. Today we know very little about the mechanisms of learning. Some parts of the brain, such as the temporal parietal and frontal lobes of the cortex, doubtless play a more important role than others (the spinal cord; retinas, occipital lobes). Learning almost certainly involves changes in efficacy of transfer of information across synapses. It involves a fast transient component and a slower consolidation component. But beyond these things very little is known, especially about the changes that occur at the synapse, or how they occur.

The second subject that interests most neurobiologists concerns the origin of specific neural connections. There are countless examples in the brain in which two gigantic structures, each with millions of nerve cells, are connected by a cable, one-way or two-way, that interconnects the cells in an incredibly specific manner so that any tiny region of one becomes closely associated with some tiny region of the other. A vivid example is the optic nerve, a bundle of just over 1 million nerve fibers that link the retina with the brain, specifically with two grape-size nests of cells deep in the brain called the lateral geniculate nuclei, and the optic radiations, which connect the lateral geniculate nuclei to cerebral cortex. The optic nerves in mammals are one-way, eye-to-brain; the radiations are two-way with some fibers carrying messages from geniculates to cortex and others carrying messages back. Each cable contains in the order of a million nerve fibers.

When the brain develops each of the structures (retina, geniculate cortex) develops by itself up to some point; then fibers grow out of the cells, bundle together and proceed to their targets, a distance of many centimeters. They do so with all the precision that exists in the fully developed brain. How each fiber knows exactly where to go is one of the great unsolved problems of neurodevelopment. Several very different kinds of theories exist, each with fairly strong experimental support, but none of them, given the present state of the subject, seems fully compelling. Everyone at least agrees that the brain wires itself up, and does so with an almost unbelievable precision. The question is a fascinating one, even if at the moment the field is rather a mess.

A curious feature of many of these fiber bundles concerns the frequency with which they are crossed – that is, they originate on one side of the brain and end up on the other. For example, as almost everyone surely knows, the left side of our cerebral cortex governs movement of the right face, arm and leg; things happening to the left of where we are looking produce a reaction in both of our eyes, but in our right lateral geniculate bodies and occipital lobes. Sounds coming from one side and arriving at our two ears at slightly different times and at different intensities, by an elaborate process of interaction have their main effects on the opposite side of the brain. The rule is not invariable: the left side of the cerebellum governs movement of the left side of the body. Nevertheless it turns out, reasonably, that the left side of the cerebellum is closely connected to the right side of the cerebral cortex, by a massive cable that crosses over from the left side to the right. But why all this crossing? No one would have imagined a priori that the left brain governs the right body, to the extent that it does. It is astonishing, and seems quite unnecessary, irrational, uncalled for, even silly. It does exist, however, and the truth is that no one has any good idea why. It is easy to predict the existences of certain crossed paths in any nervous system – consider the examples given earlier of a poked worm arcing away from the stimulus. Something like that rudimentary reflex has been advanced as explaining all the subsequently evolved crossing fibers in the nervous system. Most people find the idea possible, but not very compelling.

Now finally I want to turn to the cerebral cortex, a structure that exists except in rudimentary form only in mammals, and which in going from the lowly marsupial to man expands in a more spectacular way than any other part of the brain. The cortex happens to be the part of the brain I work on, and virtually the only part that I can talk about from first-hand experience.

Francis Crick, and for all I know others before him, has made the general statement that aggregations of cells in the nervous system can be divided into two main categories, plates and globs. There are many examples of plate-like structures, but the cortex of the cerebrum happens to be the most imposing. Spread out, the cerebral cortex occupies an area of about ½ square meter; its thickness is 2 mm. It is packed with cells, some 100,000 under each mm^2 of surface, and the cells are aggregated into six or so layers, which differ in the kinds of neurons that each contains, their form, packing densities, and their connections.

The ½ m^2 sheet is itself subdivided probably into a hundred or so regions, whose functions and connections differ profoundly from one to the next. These include about 8 or 10 separate visual areas and about as many auditory, motor, sensory (touch) and speech areas, and certainly a host of others whose functions are known vaguely or not at all. Within any one of these areas the machinery seems to be relatively constant: one millimeter is about the same as the next, and carries out the same tasks. The best known of these areas have topographic maps – a term I have touched on earlier. In our visual system one part of the visual world (say, up and to the left of where we are looking) connects to and activates one part of the visual cortex, another part of the visual world activates another.

Information reaching any one small part of the cortex is disseminated across the cortex by neuronal connections over a distance of a few mm at most. Thus in the case of vision, signals related to what is happening in one part of the visual environment arrive at the visual cortex, undergo some kind of analysis or transformation, and leave, with no interaction with what takes place in remote parts of the visual field. I speak here just of the primary visual cortex, a region about 2000 mm^2 in extent, at present the best understood region of the cortex. Here we know quite well what happens to the information between its arrival and departure. To discuss it would take all of a second hour, or a separate paper.

That, at any rate, is the kind of thing the cortex is, and does. It represents things (visual, auditory, ideational, and who knows what else?) in two-dimensions, and it makes local operations on information – to use a rather unhappy jargon.

Once invented, in the course of evolution, the cerebral cortex obviously caught fire and took off, reaching its peak in primates and, in particular, in man. For a structure that is so similar throughout its extent, it serves an astonishingly large variety of functions; as an all-purpose device it outdoes any computer and certainly anything else in the known universe.

There are great differences in the levels of our understanding of different areas of the cortex. The primary visual cortex is the only area where there exists a known difference between the information entering and leaving. For about a dozen other areas something is known descriptively about how cells behave, and beyond that our knowledge varies from vague to zero. For example, certain areas in the left hemisphere of man are well known to be involved in language, including speech, comprehension, and reading. But exactly what goes on in these regions is not understood at all. For many other areas, the functions are not known even in any global sense.

Perhaps one should ask in concluding what the future limits may be in the evolution of the brain, or if you wish, of the cortex. How far can the development go? How big, how much more complex, can it get? In the first place, to me it is far from clear what, if any, the relationship is between brain size and intelligence. Among animals of the cat family (lions, tigers, cats and so on) generally the bigger the animal, the bigger its brain. A lion's brain looks just like a magnified cat brain. It hardly seems likely that intelligence is related in any way to animal size. A lion may be smarter or more agile or better in some other way than a cat, but I know of no evidence for this. The same thing applies to members of the primate family. Perhaps bigger animals have bigger brains simply because there is room; it's not clear to me what good it does them. Of course this law breaks down completely when we compare brains of different families of animals. In general, primates tend to have bigger brains than brains of carnivores, and here there is an obvious correlation with intelligence. Whales have enormous brains, about the size of the human brain, and whales are undoubtedly very intelligent.

One anatomist friend of mine has suggested that an important limitation to the size of our brain may simply be the size of the female birth canal. Certainly in any normal delivery the head is what offers the most difficulty. Human head and brain grow considerably after birth. Thus the fact that humans, compared to other mammals, are so immature and helpless at birth may be partly explained by the problem of delivering a head of ever increasing size.

In the past few months I have had (after resisting it for years) to learn how to work a computer, and have spent more time than I like to admit writing programs. I have noticed that as one works on a program, adding to it, trying to debug it and refine it, there comes a time when the whole thing gets so cumbersome and unwieldly that it has to be torn down and built up again, often with a quite different basic design. One can't help wondering if similar problems do not arise in brain evolution. How many structures of a seemingly bizarre form owe their presence to some blind alley in evolution that has had to be abandoned? There are some suggestions that this happens. The nerve bundle that supplies our face runs in a path in the brain, before leaving it, that displays a most extraordinary loop whose presence is easily understood in terms of development. A rather large structure in our brain concerned with movement called the caudate nucleus (it degenerates in Parkinson's Disease) is rather glob-like and compact in lower animals. In man, because of the way the brain enlarges late in development, backwards, downwards and forwards, this poor structure becomes deformed almost to the shape of a pretzel. Such aberrations are gross ones, and hence easy to detect; we have no idea at all whether the detailed circuits involving information processing get into similar contortions.

There is one curious kind of apparent constraint in brain size and behavioral repertoire. The spider monkey has an extremely dexterous prehensile tail, whose ventral surface lacks hair and possesses ridges closely resembling fingerprints. The first time Torsten Wiesel and I experimented with a spider monkey, we caught it and I held the legs, Torsten held the arms and he began to inject the anesthetic. Out of nowhere came the tail, seizing the syringe out of Torsten's grasp and waving it on high, wrapped around it like a boa. The spider monkey also has feet that look like hands, with an apposable thumb that is far more dexterous than our big toe. But it pays for these assets. When you look at the hand, you see no thumb at all, just a mound-like prominence. Either there is only enough sensory and motor cortex for some limited number of agile parts - hands, feet, tail, trunk or beak - or else the limit is in something like the available attention span or the ability to coordinate these cortical areas.

Motor and sensory cortical areas of man are probably relatively old, in an evolutionary sense, and well entrenched. By comparison the speech or language areas are much more recently developed. Of these speech areas I find particularly interesting the parts (or part) concerned with reading. Reading, writing, understanding speech and producing it are functions that are at least to some extent dissociable, or so we are told by neurologists who study deficits after localized brain damage. The ability to read must surely be quite recent - probably even today not nearly every human learns to do it, though those who do learn may spend a lot of time at it. For those who read, what part of the brain, if any, becomes devoted to the task, and what does that region do in people who don't read at all? The question is a little bit related to the problem of whether someone like Mozart, who possesses some extraordinary abilities, pays some price by having some glaring defects.

To the entire question of where the brain came from or is going, and a host of more or less related questions, there are no very clear answers, as the past hour has probably convinced you. At most I can hope that the range of questions is greater than you might have supposed. As we come to understand the brain better, we will doubtless come to ask, and fail to answer, an even greater variety of questions about its origin.

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