Research and Perspectives in Neurosciences

Epigenetics, Brain and Behavior

Bearbeitet von
Paolo Sassone Corsi, Yves Christen

Weitere Fachgebiete > Medizin > Klinische und Innere Medizin > Neurologie, Neuropathologie, Klinische Neurowissenschaft

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DIE FACHBUCHHANDLUNG

Synaptic Epigenesis and the Evolution of Higher Brain Functions

Jean-Pierre Changeux

Abstract The epigenesis theory of development can be traced back to William Harvey (1651), who stated, in contrast to contemporary preformation views, that the embryo arises by "the addition of parts budding out from one another." The word epigenesis was subsequently used by Conrad Waddington (Nature 150:563–565, 1942) to specify how genes might interact with their surroundings to produce a phenotype. This is also the meaning we adopted in our paper, Theory of the Epigenesis of Neuronal Networks by Selective Stabilization of Synapses (Changeux et al. Proc Nat Acad Sci U S A 70:2974–2978, 1973), according to which the environment affects the organization of connections in an evolving neuronal network through the stabilization or degeneration (pruning) of labile synapses associated with the state of activity of the network. This definition contrasts with the recent and more restricted sense of the status of DNA methylation and histone modification in a particular genomic region. The synapse selection theory was introduced to deal with two major features regarding the genetic evolution of the human brain : 1) the non-linear increase in the organizational complexity of the brain despite a nearly constant number of genes ; and 2) the long postnatal period of brain maturation (ca. 15 years in humans), during which critical and reciprocal interactions take place between the brain and its physical, social and cultural environment. This theory will be evaluated and updated in the framework of the recent human/primate genome data, analysis of gene expression patterns during postnatal development, brain imaging of cultural pathways, such as those for language learning, and current views about the neural bases of higher brain function, in particular the global neuronal workspace architectures for access to consciousness (see Dehaene and Changeux Neuron 70:200–227, 2011).

J.-P. Changeux (✉)

Département de Neurosciences, Institut Pasteur, Collège de France, Place Marcellin Berthelot, Paris, 25 Rue de Docteur Roux, Paris, France
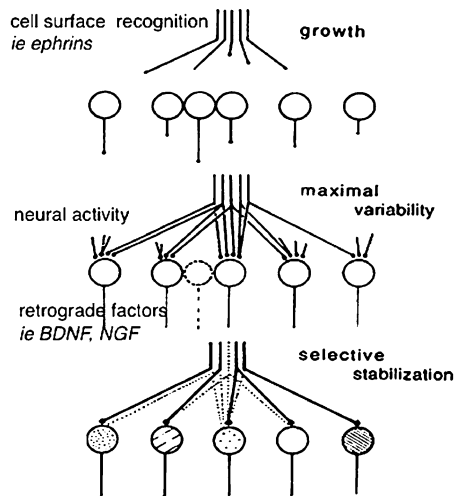
e-mail: changeux@pasteur.fr

1   Introduction

The term 'epigenesis' (or 'epigenetics') should not be seen as applying only to molecular mechanisms of chromatin modification and the regulation of gene expression. Well before the term was hijacked by molecular biologists, we had applied it to a higher level of adaptation: the selection and stabilization of synaptic connections in the central nervous system by activity, through which the animal learns to adapt to its environment (Changeux et al. 1973; Changeux and Danchin 1976). The dramatic differences in structure and function between the brains of humans and lower mammals largely result from the high proportion of the connections in the human brain that are established during post-natal life. The continuation of the epigenetic mechanisms of synaptic selection throughout life are of particular significance in humans as they both underpin and are driven by social and cultural learning. Here I review the evidence for this type of epigenesis in the developing and adult nervous system.

One essential aspect of postnatal development in the human brain is the establishment of long-range connections between different cortical areas, especially those linking the parieto-temporal-cingulate cortices with the prefrontal lobes, which are the centers for decision making, rational thinking and social interaction. According to our global neuronal workspace hypothesis (Dehaene et al. 1998), these connections are a prerequisite for accessing consciousness. We are further testing the importance of their epigenetic stabilization in two animal model systems: genetically modified mice in which genes for a nicotinic receptor subunit have been deleted and quantitative evaluation of the expression profiles and activity dependence of 12,000 genes in the rat from embryo to adult. Some of these genes are involved in the regulation of chromatin modifications, providing a bridge between the synaptic and molecular levels of epigenetic regulation.

2   Defining Synaptic Epigenesis

The term epigenesis was first applied to the nervous system in the context of the selection and stabilization of synapses during development (Changeux et al. 1973; Changeux and Danchin 1976). The growth of axons towards their targets – the dendrites of target neurons in the central nervous system or muscle cells in the periphery – involves cell-surface recognition molecules, possibly ones unique to the specific category of connections. The axon terminals branch exuberantly at first but then are pruned back in response to neuronal activity, both intrinsic spontaneous neuron firing and that evoked by external inputs. Depending on the state of activity of the target neuron, some synapses are eliminated while others are strengthened and stabilized (Fig. 1). In post-natal life, an important part of the activity in the network results from inputs from the environment and so the epigenetic selection of synapses represents learning in the network as the organism is shaped to fit its environment. In this sense, learning can be considered as a Darwinian process, because it depends on elimination of the 'unfit' synapses.

Fig. 1 Schematic representation of the hypothesis of epigenesis by selective stabilization of synapses. A nesting of many of such elementary steps occurs in the course of development. (from Changeux 1985)

cell surface recognition
ie ephrins

growth

maximal variability

neural activity

retrograde factors
ie BDNF, NGF

selective stabilization

Changeux, Courrège & Danchin (1973)

The word epigenetic was first used by William Harvey (1651), who, noting how complexity of form gradually emerges during embryogenesis, applied it to the description of how an embryo arises by "the addition of parts budding out from one another." In more modern times, the developmental biologist Conrad Waddington (1942) used the word to specify how genes interact with their sur-roundings to produce a phenotype. He conceived the concept of the 'epigenetic landscape' to illustrate how external events, some random, combine with inherited information coded in the genes to produce members of a species that, although recognizably related, have individual characteristics. His usage bridges the gap between synaptic epigenesis as defined above and the more molecularly oriented definition used in the introduction to this volume, i.e., mechanisms that permit variability beyond the Watson-Crick double helix.

One factor of considerable importance in discussing epigenetic mechanisms is that the brain is unique among organs in the specificity and number of its multiple connections between neurons (around 10^{15} in humans), a level of organization not found among, for example, the cells of the liver. Establishing and maintaining this huge connectivity requires a set of cellular processes and molecular mechanisms employed only in the nervous system.

3 Social and Cultural Evolution

Synaptic epigenesis is of particular significance in the context of the human brain because it enables social and cultural evolution (Changeux 1985). Looking at the multiple levels of variability and their timescales within the human brain, we see,

first, the variability of the genome, which underlies the biological evolution of the ancestors of *Homo sapiens* over millions of years. Next, on the ontogenetic or developmental level, is the epigenetic variability of neuronal networks and the connections that are established over days to years, depending on the species; beyond this, in humans, are the dynamics of thought, based on the variability of spontaneous/evoked neural activity and on the efficacy of synaptic connections, which operate in the 1–100 msec domain.

Finally, social and cultural evolution is associated with variable synaptic efficacy and the establishment of extracerebral memories in the form of spoken, written and pictorial material, with a time range of 100 msec to thousands of years. Spoken language and, perhaps even more significantly, writing are seminal innovations that distinguish humans from other primates; they drove the development of modern civilization and have probably also been central to the expansion of human mental capacities. Writing can be traced back to abstract cave drawings, dated around 30,000 BCE; clay counting tokens are known from Mesopotamia (9,000 BCE) and the first pictograms from Ur are from around 4,000 BCE. More important for my thesis, language and writing rely on epigenetic cultural transmission framed within a robust genetic envelope. The huge postnatal increase in the size of the human brain – the adult brain weights five times that of the newborn infant and about 50 % of the adult brain's connections develop after birth (Huttenlocher and Dabholkar 1997; Bourgeois 1997) - offers the developing brain the opportunity for intense social and cultural interactions.

Paradoxically, the evolution of the genome has lagged well behind the increase in brain complexity during mammalian evolution (Venter et al. 2001). The mouse, the rat and the monkey have approximately the same number of genes as a human (20,000-25,000). Yet the mouse has only 40×10^6 neurons, whereas the human brain contains in the range of $50-100 \times 10^9$. Gene sequences have not increased in complexity in parallel with the increase in complexity of the brain. Yet what happened? The explanation for this disparity, in my view, lies in a few genetic events that favored the prolonged and extensive post-natal increase in neuronal branching and synaptic connectivity in humans and its modulation by extended epigenetic responses to the environment.

4 Synaptic Selection and Stabilization

The extension of the post-natal period of development in humans has been essential for the genesis and internalization of culture, as well as for the acquisition and transmission of individual experience. In rats, the maximum synaptic density is reached within a few weeks after birth, whereas in humans it takes over three years. Moreover, rats show little loss of synapses after maximum density is reached, whereas in humans there is a steady decline until the total number stabilizes about the time of puberty (Huttenlocher and Dabholkar 1997; Bourgeois 1997; Petanjek et al. 2011), reflecting the initial exuberance and later pruning of
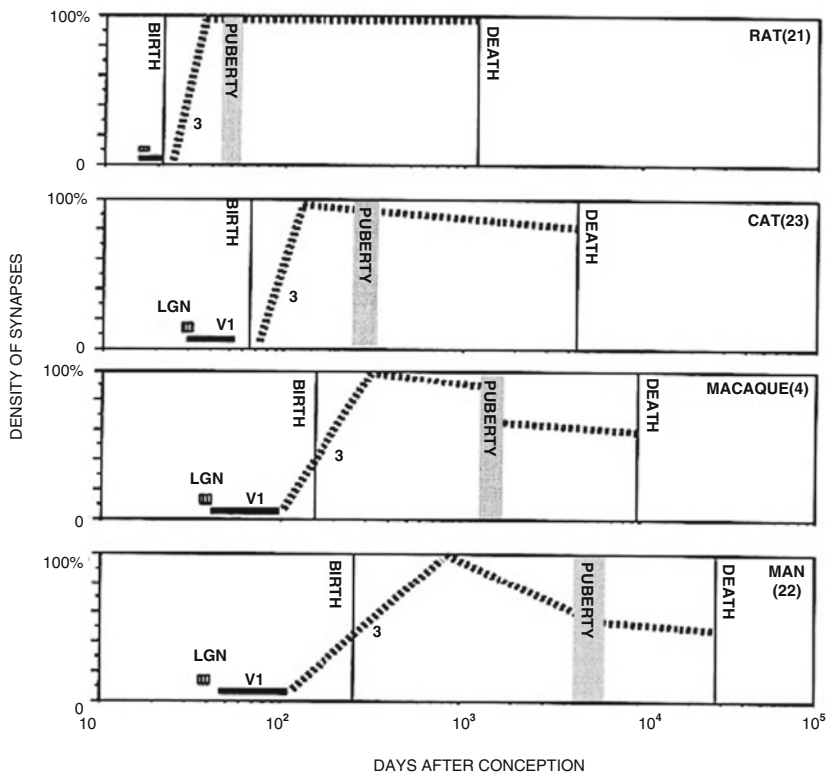
Fig. 2 Postnatal evolution of the total number of cortical synapses in different mammalian species. Note the significant decrease in the global envelope of synapses taking place before puberty in humans. (from Changeux 2004)

connections (cat and monkey show intermediate stages of this process as life span and infant dependency increase; Fig. 2). This major distinction between lower mammals and humans has to be borne in mind when using rats and mice as models for human psychiatric and neurological conditions. When *H. sapiens* appeared in Africa about 100,000 years ago, half the average life span of around 30 years would have been taken up with building the brain. And, of course, in contemporary humans, the process of synaptic refinement goes far beyond puberty: learning is lifelong (Petanjek et al. 2011).

The decline in synaptic numbers during childhood reflects learning by selection. The initially exuberant connections are refined by activity in the network as some synapses are reinforced and others are eliminated (Fig. 1). Some early demonstrations of this process include work on motor neurons innervating muscle cells (Benoit and Changeux 1975, 1978; O'Brien et al. 1977; Henderson et al. 1986; Gouzé et al. 1983; Bourgeois et al. 1986), the establishment of retinal inputs to the cat lateral geniculate body (Stretavan et al. 1988); and studies in many other systems (Luo and O'Leary 2005; Wu et al. 2012; Kano and Hashimoto 2011; Ko et al. 2011).

These and many other studies have shown that, when neuronal activity is artificially modified, synaptic pruning is altered. In particular, at variance with the classical Lamarckist-constructivist scheme (Quartz and Sejnowski 1997), blocking the activity maintains a high number of connections: it is activity that enhances synaptic elimination (Benoit and Changeux 1975, 1978; Stretavan et al. 1988; Luo and O'Leary 2005). As I have said in the past « to learn is to eliminate » (Changeux 1985).

More recent work has revealed detailed mechanisms involved in synaptic plasticity, including processes of molecular selection by changes in the diffusion dynamics of receptors in the synaptic membrane while receptors maintain a stable density under the nerve ending (Triller and Choquet 2008), and allosteric state transitions in the NMDA receptor trappping the diffusible D1 dopamine receptor that result in an increase in spines bearing dopamine receptors (Scott et al. 2006), which is a plasticity phenomenon possibly altered in neuropsychiatric disorders.

Disruption of synapse selection and connectivity can also be seen in several human neurodevelopmental disorders. For instance, various mutations linked to autism are in genes that are involved in synapse formation/stabilization, such as NEUROLIGINS 3/4, NEUREXIN 1 and SHANK 3, which code for synaptic adhesion and stability proteins (Bourgeron 2009, this volume). The dynamics of synapse stabilization is altered in Fragile X mental retardation by expanded CGG repeats in the FMR1 gene, which produces a protein that interferes with the Rac1 pathway and controls actin cytoskeleton dynamics (Mandel and Biancalana 2004; Castets et al. 2005). Changes in synaptic pruning have been associated with the onset of schizophrenia, a disease that has been linked to the susceptibility genes ERBB4, SLC1A3, RAPGEF4 and CIT28; the last is also involved in bipolar disorder (Karlsgodt et al. 2008). Links with NEUREXIN 1, which is, as mentioned, involved in synapse formation/stabilization, have also been reported (Cook and Scherer 2008).

The theory of the epigenesis of neuronal networks by selective stabilization of synapses (Changeux et al. 1973) was introduced to account for the interactions that take place between the brain and its physical, social and cultural environment in the course of development; this theory therefore accounts for the variability in the brain's connectivity and in behavior between individuals, associated with the variability of the environment. Such an epigenetic variability of brain anatomy would be superimposed on that created by the variability of the genome. Another critical feature of the theory is that, conversely and unexpectedly, it may account for the constancy of some behaviors despite epigenetic variability. The same learning input may not stabilize the same connective patterns in different individuals but nevertheless result in the same behavior.

This idea was originally stated as the 'variability theorem' (Changeux et al. 1973) that « different learning inputs may produce different connective organizations and neuronal functioning abilities, but the same behavioral abilities. » This finding is particularly evident in the brains of genetically identical individuals that, contrary to expectation, do not show identical nerve organization. To give a simple example, the exact branching patterns of identified motor neurons in a parthenogenetic fish, *Poecilia formosa*, have been established by electron microscopy. This pattern was found to vary significantly not only between genetically identical individuals

(identical twins) but also on the left and right sides of the same animal. Yet the fishes all swim the same way (Levinthal et al. 1976). Thus, to some extent, the development of the fine details of the connectivity pattern includes a stochastic element - chance plays a part in determining exactly which synapses survive - yet the behavior may nevertheless remain constant between individuals. At a much higher level of complexity, humans with language areas located either in the left or right hemispheres, or in both, are indistinguishable by the way they speak or think! There is no contradiction between epigenetic « Darwinian » selection and the occurrence of behavioral universals.

One of the critical inputs that may contribute to synapse selection is reward (Thorndike 1911; Hull 1943; Skinner 1981). Positive reward is signalled by neurons in the brain stem that release dopamine in the frontal cortex, whereas serotonin neurons signal negative reward, or punishment (Dehaene and Changeux 1991, 2000). The evolution of connectivity through selection has been tested using a network simulation that can learn to do specific tasks when given simple positive and negative rewards (Gisiger et al. 2005). Before learning, the connectivity in the network is diffuse and homogeneous and task completion is unsuccessful; after learning, the selected connections form a coherent and organized network that can complete tasks successfully. Further work should establish the actual contribution of reward to synapse selection in the course of development.

5   Epigenetics and Higher Brain Function

As already discussed, post-natal selection is essential for establishing the neuronal circuits serving culturally acquired behaviors such as writing and reading. By painstakingly reconstructing the lesions in the brains of patients with various deficits, Dejerine (1901) was able to identify a variety of defects associated with learning written language. One such lesion caused an inability to read but left writing intact, a condition called pure alexia; the reverse lesion produced agraphia without alexia. These observations can be understood as evidence for separate epigenetic "cultural » circuits" for reading and writing that are laid down in childhood.

More recently, the circuits involved in literacy have been examined using brain imaging. They confirm Dejerine's pionneering insight. These studies (Castro-Caldas et al. 1998) took advantage of behavioral evidence of different phonological processing in illiterate vs literate subjects. During repetition of real words, the literate and illiterate groups performed similarly and activated similar areas of the brain. In contrast, illiterate subjects had more difficulty correctly repeating pseudowords and did not activate the same neural structures as literates. Comparison of PET scans from illiterate and literate groups showed a considerable shift in activation. For instance, in a pseudowords–words contrast, activation in the literate group was stronger in the right frontal opercular–anterior insular region, left anterior cingulate, left lentiform nucleus and anterior thalamus/hypothalamus compared with the illiterate group (Castro-Caldas et al. 1998; Carreiras et al. 2009).

The connectivity used for reading and writing can thus be seen as an epigenetic appropriation of existing circuitry. Scans from ex-illiterates showed substantial similarity to those from literates, showing that the ability to acquire these cultural imprints persisted into adulthood (Dehaene et al. 2010).

Among the cortical connections established in post-natal life are the long-range tracts between the frontal areas and other brain cortical areas (including sensory ones) that determine and organize action (see Pugliese et al. 2009). Some years ago, we proposed that these long-range connections, by broadcasting signals to multiple brain areas, yield subjective experience (Dehaene et al. 1998; Dehaene and Changeux 2011). We termed this the 'global neuronal workspace' hypothesis: by allowing sensory inputs – seeing, hearing and so on – global access to many brain areas, the long-range connections provide a structural basis for the global experience known as conscious access.

Long-range connections mostly originate from the pyramidal neurons in cortical layers II and III and are specially abundant in the prefrontal cortex (von Economo and Koskinas 1925). Particularly important are the connections with the prefrontal areas, the part of the cortex involved in planning, decision making, thought and socialization, that have evolved most dramatically between mice and humans (for a more detailed review of the global neuronal workspace hypothesis and its applications, see Changeux 2006; Changeux and Lou 2011; Dehaene and Changeux 2011).

One question we are currently asking is whether these long-range connections are especially vulnerable to some pathologies. As mentioned above, the onset of schizophrenia has been linked to susceptibility genes coding for several proteins involved in synaptic pruning (Karlsgodt et al. 2008; Cook and Scherer 2008). Significantly, the long-range connections might be affected differentially by susceptibility mutations that are known to affect synaptogenesis in general (Scott-Van Zeeland et al. 2010). This vulnerability might result, for instance, from a very low nucleo-cytoplasmic ratio and/or changes in the long-distance transport of essential cellular components along the axons, which could explain the specificity of the schizophrenic phenotype as distinct from the mental retardation expected from a global deficit in synaptogenesis.

One way we are testing this vulnerability is by comparing the dendritic branching of pyramidal neurons in wild-type mice with animals lacking the β2-subunit of the nicotinic acetylcholine receptor (Ballesteros-Yáñez et al. 2010). Loss of this subunit prevents the high-affinity binding of the neurotransmitter acetylcholine and, as a consequence, mice lacking the β2-subunit show a characteristic behavioral deficit: their exploratory drive, which is one of the most cognitive aspect of mouse behavior, is reduced, although their navigation abilities, a more automatic activity, are unaffected. Even though establishing a fair analogy between mouse behavior and human psychology may look far-fetched, it has been hypothesized that the mice might possibly be showing an alteration in elementary conscious access (see Avale et al. 2011; reviewed in Changeux 2006).

So far, we have not been able to examine the long-range projections but we have measured the complexity of the basal dendrites of 650 neurons from layer III in seven areas from the cortex of wild-type and β2−/− mice. In agreement with

Elston's (2003) work on the monkey, the neurons in the wild-type mice show a gradient of complexity: those in anterior areas have longer dendrites, larger dendritic fields and more spines. Such a complexity gradient may be interpreted in terms of the global neuronal workspace hypothesis as resulting from denser long-range connectivity originating from prefrontal areas. In contrast, the neurons in the knock-out mice are fairly uniform throughout the cortex, implying that the neurons in the frontal areas are not receiving as many inputs from the sensory areas as they do in the wild-type animals. In other words, the lack of nicotinic receptor activation seems to epigenetically enhance a selective loss of long-range connectivity.

These studies on mice may be relevant to a possible effect of chronic nicotine use on long-range connectivity. In humans, diffusion tensor imaging, which allows the meaurement of the location, orientation, and anisotropy of the white-matter tracts in the brain, has shown reduced integrity in the frontal white matter in people who are cocaine dependent or who abuse heroin. The same method has revealed that prenatal and adolescent exposure to tobacco smoke alters the development of the microstructure of the white matter, with increased fractional anisotropy in right and left frontal regions and in the genu of the corpus callosum (reviewed in Changeux and Lou 2011). These observations suggest that nicotine may also act directly on white matter and there is electrophysiological evidence that supports a direct action of nicotine on axon conduction, possibly at the level of the node of Ranvier (reviewed in Changeux 2010). Thus there is support for direct control of the global neuronal workspace by nicotine at the white matter level. This work further implies that drugs of abuse like nicotine may interfere with the functioning of the long-range cortical connections, so addicts may lose some conscious control of their actions.

6 Where Next?

We are turning back to the conventional tools of molecular genetics to map the expression patterns of genes involved in synaptic epigenesis throughout the life span of the rat. Using chip technology, the changes in expression of 12,000 genes in the cortex have been analyzed by computational methods at stages from embryonic day 16 through birth, puberty and adulthood to old age at post-natal day 90 (Tsigelny et al. submitted). One dramatic change is at birth, when many genes active in the embryo are switched off and thousands of other genes become active, just as the animal goes through the most radical change in its environment that it is ever likely to encounter.

One fascinating aspect of this study is that some of the activated genes are involved in the regulation of chromatin modifications, which links the level of synaptic epigenesis that I have been discussing here back to the molecular mechanisms that are being detailed by other contributors to this volume.

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