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CHAPTER 2 (in O. Houdé & G. Borst (Eds.), 2021, The Cambridge Hanbook of Cognitive Development)

Epigenesis, synapse selection, cultural imprints, and brain development: from molecules to cognition

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1. Introduction: the singularity of brain organisation and synaptic epigenesis

The human brain is, neither John Locke's "blank slate" deprived of any pre-existing innate structure – or, in a modern AI language, a random network of undifferentiated neurons fully instructed by experience – nor a fully genetically determined, irrevocably hard-wired neuronal architecture. Neither is it represented by the simplistic yet very popular deep-learning artificial networks. The 85 to 100 billion neurons of the human brain and their synaptic connections, that arose over million years of evolution and for each individual brain over almost 15 years of postnatal development, possess an original organisation unmatched by any of our current computers. It is a unique compromise between an eminently variable, intrinsically rich, connectivity and a set of species-specific, genetically determined, rules, which unambiguously make our brain that of Homo sapiens.

From a systemic point of view, the brain may be described as a dynamic assembly of multiple functional and reciprocally inter-regulated levels of structural organisation, bottom-up, from molecule to consciousness and, conversely, top-down from cognitive functions to molecular processes, unified in a single global system. Actually, the brain may be viewed as the seat of multiple nested spontaneous evolutions operating concomittantly through variation-selection-amplification ("Darwinian") mechanisms (Changeux et al., 1973; Changeux & Danchin, 1976; Changeux, 1983, 1985; Morange et al., 2016; Edelman, 1987, 2006; Barkow et al., 1992; Campbell, 2016). These evolutions develop on strikingly different time scales: from the million years of the descent of man

up to the 100 ms of psychological processes. They further operate from diverse variable units distributed in parallel at multiple nested levels of physical organisation through variation-selection-amplification mechanisms creating profound inter-twinnings between the developing (and adult) neuronal organisation of the brain and the constantly evolving physical, social, and cultural environment. Brain's morphogenesis is progressive, with forms becoming intricated within forms, including possibly, at each step, sensitive phases of interactions with the environment. This dual relationship between the developing brain and its environment introduces an essential variability in the anatomy and functional architecture of the brain, which makes any individual human brain unique from both a connectional and behavioral point of view (Changeux, 2017).

The aim of this chapter is to present and discuss a theory – initially expressed as a mathematical model (*A Theory of the Epigenesis of Neuronal Networks by Selective Stabilization of Synapses,* Changeux, Courrèges, Danchin, 1973) – that gives access to such "epigenetic" inscription of environmental features within the developing connectivity of the brain. These views were consistent at the time with the behavioral observations of the newborn "learning by unlearning" (Mehler 1982) and with the then available knowledge of molecular biology. They did not need to refer to any sort of «instructive» or so-called "Lamarckian" mechanism (Quartz & Sejnowski, 1997; Piaget 1976). Furthermore, the term "epigenesis" (or "epigenetics"), was used, in a sense close to its original definition by Waddington (1942), and to his concept of the "epigenetic landscape" to illustrate how external events, some random, combine with inherited information coded in the genes to produce acquired variability between individuals from the same species. A well-established case is the acquisition of oral and written language, which, as discussed below, leaves important connectomic traces in the brain, which are re-learned, from one generation to the next.

This meaning differs from the concept of DNA "epigenetics" subsequently used in molecular biology to refer to unrelated mechanisms of

DNA covalent modifications such as methylation and/or chromatin remodeling which contribute to the regulation of genes expression without altering the DNA sequence (Lucchesi, 2019). The long-term heritability of such phenotypic changes has been suggested but heavily questioned. In addition, DNA "epigenetics" deals with gene expression at the level of the single nucleus of the nerve cell while each individual neuron may establish up to 10 to 100 000 synapses available for synaptic epigenesis. Several levels of brain organization thus distinguish restricted DNA "epigenetics" from a broader synaptic epigenesis.

In the brain, the macromolecular level holds a decisive role by imposing inescapable bottom up physical constraints upon higher – up to the highest – functions (Changeux, 1983, 1985, 2017). First of all, the evolution of the species-specific features of the brain is grounded in the genes of the organism – in particular those which determine the "proto-organisation" (Rakic, 1976; Geschwind & Rakic, 2013; Arcaro & Livingstone, 2017) or scaffolding of human brain connectivity – that we have referred to as the "genetic envelope" (Changeux, Courrèges, Danchin, 1973). Yet, the issue of the evolution of the genetic envelope compared to the brain phenotype raises an interesting paradox. From mouse to humans, the size of the brain and, in parallel, its total number of neurons, increases from approximately 40-70 million to 85 billion (plus 50 billion glial cells), and the number of specialised cortical areas per hemisphere raises from about 10 in primitive mammals to as many as 180 in humans (Markov et al, 2013). In addition, the intrinsic connectivity, especially in the cerebral cortex, dramatically increases in diversity leading to the ultimate development of the oral language in less than 1 million years ago (Changeux et al 2020; Goulas et al., 2019).

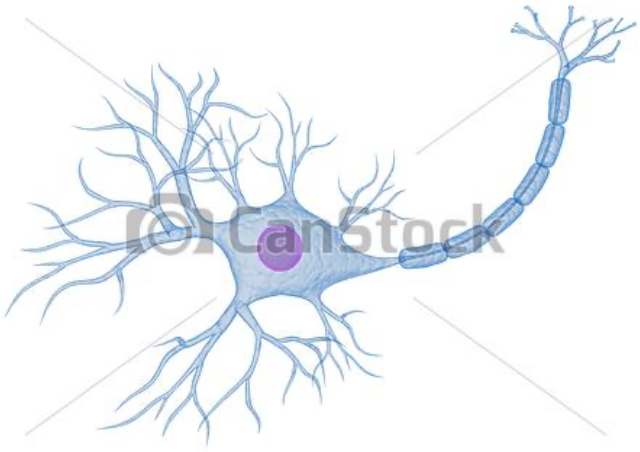
By contrast, the full genome sequences now available for many species, mouse, monkey, chimpanzee, humans, and fossil human ancestors (Paabo, 2013), are striking in their relative uniformity. The haploid genome comprises no more than about 20 000 gene coding sequences (only 1.2% of the human genome) and this number does not vary significantly from mouse to humans (Somel et al, 2013; Paabo 2013; Geschwind & Rakic 2013;

Vallender et al 2006). The coding genome itself appears highly conserved, especially for brain proteins, even at the most recent stages of hominisation. The available comparative genomic data unambiguously reveal that the observed increase of brain anatomical and functional complexity does not reflect a parallel increase in the complexity of the genome (Dumas et al, 2019). This may be seen as an "astonishing evolutionary parsimony" (Changeux 1983, 1985, 2017, Changeux et al 2020). Still, at this stage, the actual few discrete genetic regulatory events that determined the fast increase in brain complexity during the past million years of hominisation remain unidentified. These might include discrete changes in genomic organization including gene duplications (Suzuki, 2018), DNA regulatory sequences (Weyer & Paabo, 2016; Petr et al, 2019) and others concerning the relationships between genes and phenotypes which have been underevaluated within the classical "one gene-one protein-one phenotype" paradigm. The selective stabilisation hypothesis is here presented as one mechanism, which might contribute to this evolutionary parsimony (Changeux 1983, 2017, Changeux et al 2020).

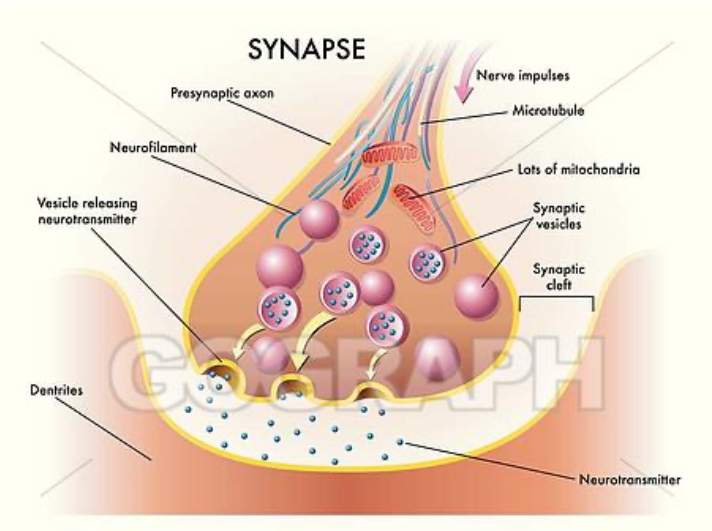
2. The model of Changeux-Courrège-Danchin (CCD), 1973

During embryonic and postnatal development, the million billion synapses that form the adult human brain network do not assemble, like the parts of a computer, according to a plan that defines with great precision the disposition of all individual components. If this were the case, the slightest error in the instructions for carrying out this program could have catastrophic consequences. The mechanism proposed, on the contrary, relies upon the variability of developing interneuronal connections (within the mentioned genetic envelope) and the progressive setting of robust synapses through trial-and-error mechanisms that formally resemble an evolutionary process by variation-selection (Changeux, Courrège, & Danchin, 1973; Changeux & Danchin, 1976; Rakic, 1976; Edelman, 1978; Shatz & Stryker, 1978; Purves & Lichtman, 1980; Blakemore et al., 1981; Bourgeois et al., 1986; Rakic et al., 1986; Sretavan et al, 1988; Kasthuri & Lichtman, 2003; Arcaro & Livingstone, 2017; Changeux, 2017). A most important and unique feature of human brain evolution is the extension of postnatal development for up to 15 years. An approximately five-fold

increase in brain weight accompanies this development, during which about half of all adult synaptic connections are formed at a very fast pace (approximately 0.5 million synapses per second) (Lagercrantz et al, 2010). The model was essentially designed to apply for the postnatal period of synaptogenesis of the human brain but may also account for some earlier steps of prenatal synaptogenesis and for the adult brain yet to a lower extent (Petanjek et al., 2011).



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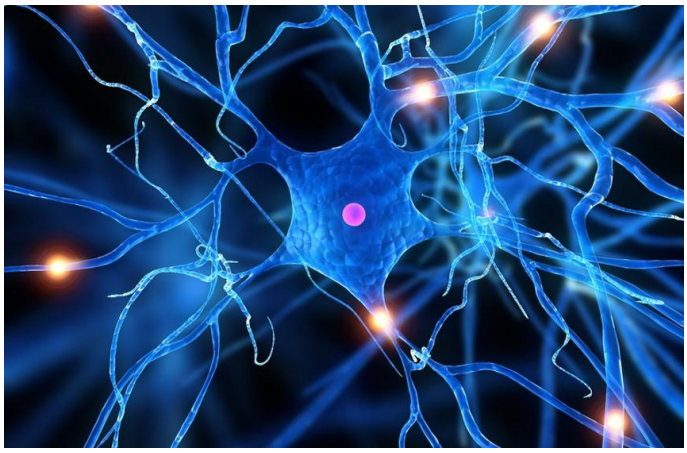


Fig.1. The neurone and the interneuronal connections through the synapse in the human brain.

On formal grounds, the original concept (CCD model, 1973) has been extended with the "neural darwinism" (Edelman, 1978), the group-selection theory of higher brain functions (Edelman, 1981) and more recently with the theory of symmetry breaking in space-time hierarchies (Pillai & Jirsa, 2017), among others.

The CCD model is based on the principle that interneuronal contacts, the synapses, mediate information transfers through the system. At nested critical periods during the development of the brain, the phenotypic variability of nerve cell distribution and position, as well as the exuberant spread and the multiple transient connectivity configurations resulting from the growth cone wanderings, produce a broad diversity of synaptic connections. This transient diversity is then reduced by the selective stabilisation of some of the labile contacts and elimination (or retraction and/or pruning) of others. Excitatory as well as inhibitory synapses may exist under at least three connective states: Labile (L), Stable (S), and Degenerate (D); only states L and S transmit nerve impulses and the acceptable transitions between states are L—>S L—>D and S—>L. A critical implication of the model is that evolution of the connective state of individual synaptic contacts is governed globally, and within a given time window, by the total activity afferent onto the postsynaptic soma during a prior time interval of determinate length (evolutive power of the soma). It includes, as a particular case, the standard Hebbian time-coincidence relationship and the popular statement "cells that fire together wire

together". Activity of the postsynaptic cell in turn regulates, in a retrograde manner, the stabilisation and/or elimination of afferent synapses.

The maximum wiring and the main stages of development of the network of synaptic connections, as well as the evolutive power and the integrative power (after the usual "firing" mechanism) of each soma is a determinate expression of the genetic endowment (the "genetic envelope" of the network). The emergence during growth of a large number of labile synapses is provided by this species specific envelope. The associative property that results from the "learning process" is structurally printed as a particular pattern of such organization. This pattern results often from the selection by functioning of particular pathways among a large number of labile synapses (especialy during growth). Such trial-and-error mechanisms formally resembles the variation-selection process of an evolutionary Darwinian but epigenetic process (Campbell, 2016) (see Fig. 2).

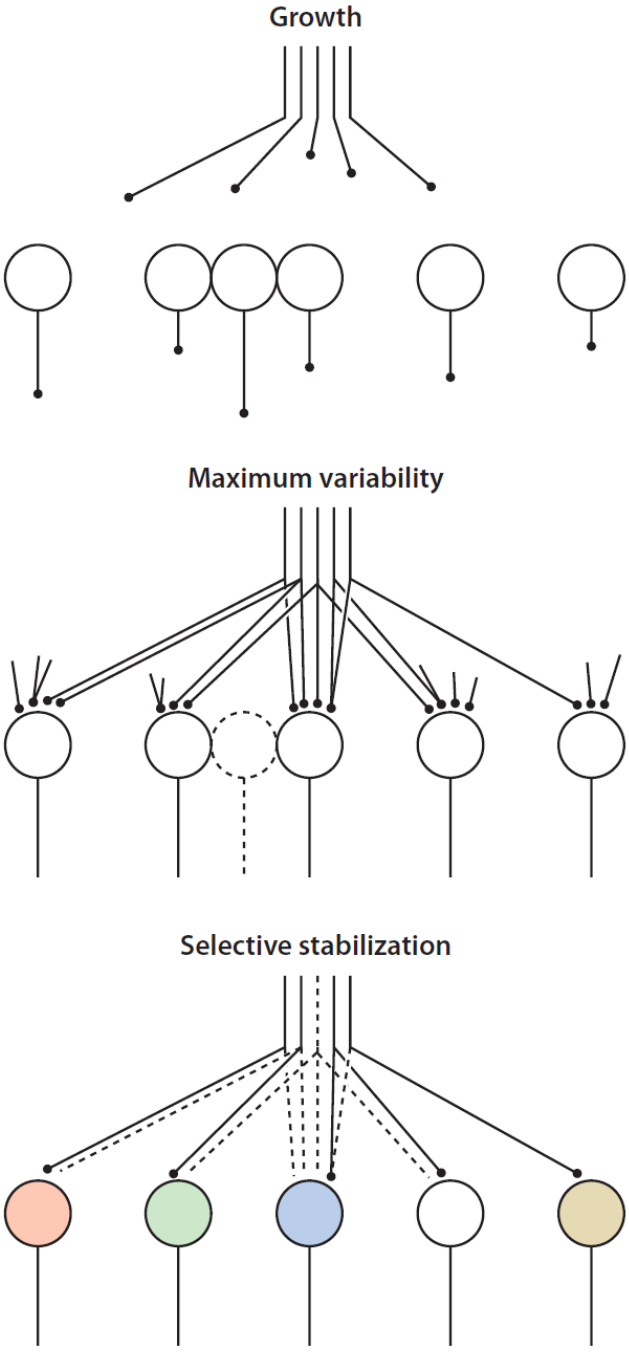


Fig. 2. Schematic representation of the hypothesis of epigenesis by selective stabilization of synapses (from Changeux, 1983, 1985). A nesting of many of such elementary steps occurs in the course of development. The growth of axons towards their targets – the dendrites of target neurons in the central 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, depending on the state of activity of the target neuron – both intrinsic spontaneous firing or evoked by external inputs – some synapses are eliminated (pruned) while others are strengthened and stabilized. 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.

3. **The variability theorem and the "multiple realisability" of brain functions**

The CDD model or theory accounts for the interactions that take place between the brain and its physical, social and cultural environment in the course of cognitive development. But it accounts in addition for a property largely under-evaluated in brain research: the variability in the brain's connectivity and in behavior between individuals, which is associated with the variability of the environment and would be superimposed on that created by the variability of the genome.

As mentioned, in the course of the proposed epigenesis, diversification of neurons belonging to the same category occurs by the acquisition of the precise pattern of connections it establishes (and neurotransmitter/receptors it synthesizes) (Changeux, 1983, 1985). An unexpected but critical feature of the theory is that it may account for the constancy of some behaviors despite such epigenetic variability of the connectivity. This idea was originally stated as the "variability theorem" (CCD model, 1973) that "different learning inputs may produce different connective organizations and neuronal functioning abilities, but the same behavioral abilities". Thus, the neuronal connectivity code exhibits "degeneracy" (see Edelman, 1978; Edelman & Gally, 2001; Tononi et al., 1999), that is, different code words (connection patterns) may carry the same meaning (function).

One prediction of the variability theorem is that the synaptic connectivity of genetically identical individuals (i.e., monozygotic twins) may display phenotypic variance. This was initially demonstrated using serial electron microscopy scans of genetically identical individuals (identical twins). In the small invertebrate Daphnia magna, the number of cells is fixed and the main categories of contacts (between optic sensory cells and optic ganglion neurons) are preserved from one isogenic individual to another. Yet, the exact number of synapses and the precise form of the axonal branches varies between pairs of identical twins

(Macagno, Lopresti, & Levinthal, 1973). Similar findings have been reported in the case of the Müller cells of a parthenogenetic fish (Poecilia formosa) (Levinthal, Macagno, & Levinthal, 1976) and thus they are not restricted to invertebrates. In a general manner, a phenotypic variance of the connectivity exists. This has been exquisitely demonstrated in the rat where a detailed left–right comparison of interscutularis muscle innervation by the same motor-neurons (Lu, Tapia, White & Lichtman, 2009) revealed a profound variability of axon branching. This has been confirmed with the nervous system of isogenic Caenorhabditis which was until recently viewed as precisely wired up to the individual synapse level (Oren-Suissa et al, 2016). Yet, the Daphnia, the worm, the fish, individuals all swim similarly, and the left and right limbs of the rat also work the same!

In mammals, the variation also affects the number of neurons. For instance, in the case of the cerebellum of the mouse, the division and migration of Purkinje cells in consanguineous strains are not subject to as rigorous and precise a determinism as the laying down of neurons in invertebrates (Oster-Granite & Gearhart, 1981; Goldowitz & Mullen, 1982). The variability becomes microscopic and may even affect its chemistry, such as the type of neurotransmitter through activity dependant switches (Spitzer, 2017) or the pattern of transmitters and coexisting messengers synthesized (Hokfelt et al., 1986, 2018) of entire populations of neurons.

At a much higher level of complexity, humans with language areas either located in the left or right hemispheres, or in both, are indistinguishable by the way they speak or think! In monozygotic twins differences in manual preferences have even been discovered which by itself is a sign of variance at the behavioral level. In vivo measurements using magnetic resonance imaging of the planum temporale further reveal brain images that differ between the left- and right-handed twins with a difference, which is more pronounced in the right-handed one (Steinmetz et al, 1995; Sommer et al, 2002).

In humans, most of the information available on anatomy derives from individuals taken from genetically heterogeneous populations.

Nevertheless, even under such conditions, the substantial variability noticed, and thus, the development of the fine details of the brain connectivity pattern, is expected to include a stochastic element. Chance plays a part in determining exactly which synapses survive. Nevertheless, the behavior may remain constant between individuals. These views are consistent with recent formal description of brain behavior as a low-dimensional process emerging from a network's dynamics depending on the symmetry and invariance properties of the network connectivity (Pillai & Jirsa, 2017). These authors show that given behavioral patterns can be accomplished through the use of distinct architectures utilizing (at least partly) different functional modes (engaging the same or different neuro-muscular linkages) (Perdikis et al., 2011). They conclude that since the different control structures are likely to draw on distinct neural network components, this prediction speaks to the concept of degeneracy, which is precisely what we proposed as "variability" in the early formulation of the CCD theory (1973). There is no contradiction between epigenetic "Darwinian" selection and the occurrence of behavioral universals. The synapse selection model offers a neural example to "multiple realisability" – that is, the non-unique (degenerate) mapping of a given "invariant" function to the underlying neural organisation (CCD 1973; Pillai & Jirsa, 2017). This let some cognitivist philosophers incorrectly either "believe" that, in particular because of this degenerate mapping, the attemps to define precise relationship between the connectional organisation of the brain and its cognitive – in particular language – abilities is irrelevant (Fodor 1983) or even might remain a "mystery" for ever (see Chomsky in Hauser et al., 2014).

4. Cellular and molecular mechanisms of synapse selection

Both the spontaneous and the evoked activity may contribute to the synapse selection process. In this framework, the suggestion was made that reward signals received from the environment may control the developmental evolution of connectivity (Thorndike, 1911; Hull, 1943; Skinner, 1981; see

also Gisiger et al., 2005; Gisiger & Kerszberg, 2006). 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 & Changeux, 1991, 2000; Kobayashi & Schultz, 2014; Stauffer et al., 2016). 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 largely diffuse and unstructured and task completion is unsuccessfull. After learning, the selected connections form a coherent and organized network that can complete tasks successfully. This is illustrated in the case of a visual delayed-matching-to-sample (Gisiger et al., 2005) or in a logical reasoning task (Houdé et al., 2000) both involving a prefrontal network. Further work should establish the actual contribution of reward to synapse selection in the course of development.

The cellular and molecular mechanisms involved in synapse selection are rather diverse. They include GABAergic inhibition, which contributes to the 'opening' of the critical period where synapse selection occurs (Hensch, 2005; Werker & Hensch, 2015). A shift in the excitatory–inhibitory balance is associated with the maturation of fast-spiking GABAergic inhibitory neurons that synthesise parvalbumin and are localised in layers III/IV of the cerebral cortex (Takesian & Hensch, 2013). Pharmacological agents that accelerate GABAergic circuit function (such as benzodiazepines acting as positive allosteric modulators of $GABA_A$ receptors) elicit precocious onset, whereas genetic manipulations (such as the deletion of genes involved in GABA synthesis) or environmental disruption (such as dark rearing or hearing loss) lead to a delay of the critical period.

During early postnatal development, microglia undergo morphological maturation that matches synaptic maturation and possess phagocytic properties which led to the hypothesis that microglia may have a role in the elimination of exuberant synaptic connections during development. This hypothesis is supported by studies that reported the appearance of excess immature synapses in mice lacking either the fractalkine (Cx3cl1/Cx3cr1) or complement component (C1q/C3/CR3) microglia signaling pathways (Paolicelli et al, 2011; Weinhard et al, 2018).

Following gene expression in the course of synapse selection in the visual system, it was found that among the genes regulated by neural activity are the MHC (major histocompatibility) Class I family genes (Corriveau, Huh & Shatz, 1998). This finding was rather unexpected because these genes – HLA genes in humans – are involved in cellular immunity and were previously not thought to be expressed by neurons. Other components of a signaling system for Class I MHC are also present in neurons, including their receptor, PirB (Kim et al, 2013). The study of mice deleted for theses diverse molecular components revealed that they are required for activity-dependant synapse selection (Huh et al, 2000). Homologs are present in the human brain and may have some relevance for understanding brain wiring developmental disorders including Alzheimer disease (Kim et al., 2013).

Neurotrophic factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), and neurotrophin-3 (NT-3) (Mandolesi et al 2005), are important regulators of visual cortical plasticity (Huang et al., 1999). In transgenic mice in which the postnatal rise in BDNF in the forebrain was genetically accelerated, a precocious termination of the critical period of ocular dominance plasticity was found, which correlated with an accelerated maturation of GABAergic inhibitory circuitry. Neurotrophic factors are important modulators of synaptic epigenesis and brain development in general.

In addition, homeoproteins, such as Otx2, have been reported to have a role in synaptic evolution during critical periods of development (Prochiantz & Di Nardo, 2015). For instance, Otx2 accumulates in an activity-dependant manner inside the fast-spiking GABAergic neurons. Intriguingly, Otx2 is not expressed by these cells but instead is imported through diffusion from one or several external sources (Spatazza et al., 2013). Therefore, it was proposed that, in the mouse, Otx2 accumulation by fast spiking neurons cells is necessary and sufficient for a binocular critical period opening at 20 days after birth and closing at 40 days (Prochiantz & Di Nardo, 2015).

Other work has revealed detailed mechanisms involved in synapse selection at the molecular level. Activity-dependant changes in the diffusion

dynamics of postsynaptic receptors present under the nerve terminals have been recorded even if the density of receptors remains stable under the nerve ending (Triller & Choquet, 2008). Also, allosteric transitions of the NMDA receptor trapps the diffusible D1 dopamine receptor resulting in an increase in dendritic spines bearing dopamine receptors (Scott et al, 2006). Such plasticity phenomena might possibly be altered in neuropsychiatric disorders.

Several molecular and cellular mechanisms are available for the active selection process to take place. They are themselves under stringent genetic control and belong to the genetic envelope of the species.

5. **Anatomical and physiological evidence supporting the selective-stabilisation of synapses model**

The classical Wiesel and Hubel experiments with the cat about the effects of monocular deprivation on binocular vision are consistent with the selective stabilisation hypothesis (Hubel & Wiesel, 1965; Shatz & Stryker, 1978; LeVay et al., 1980; Sretavan et al., 1988). If, during a critical period in early life, one eye is allowed to see normally, whereas the vision of the other eye is occluded most of the cortical cells, even those in the deprived eye's columns, lose their ability to respond to the deprived eye (Wiesel & Hubel, 1963; Hubel & Wiesel, 1970; Hubel et al., 1977; Shatz & Stryker, 1978). This physiological loss of response is followed in 1 week by a dramatic retraction of the branches of deprived geniculocortical arbors and is later followed by a compensatory expansion of the arbors of the open eye (Rakic, 1976; LeVay et al., 1980; Antonini & Stryker, 1996). The effects of deprivation can be reversed to a limited extent during the critical period but they later become irreversible (Wiesel & Hubel, 1965; Movshon, 1976; van Sluyters, 1978; Blakemore et al., 1981; Antonini & Stryker, 1998). An example of such irreversible effect of epigenetic experience in humans is amblyopia, an eye disorder characterized by an impaired vision in one eye that otherwise appears normal. It may be viewed as a "cortical blindness" that occurs during early childhood, as a consquence of cataract or strabysmus.

Early demonstration of the process of synapse stabilisation accompanied by synapse elimination of supernumerary nerve endings include work on motor neurons innervating skeletal muscle cells (Benoit & Changeux, 1975, 1978; O'Brien et al., 1977; Henderson et al., 1986; Gouzé et al., 1983; Rakic et al., 1986; Turney et al., 2012). In the adult, there is only one motor nerve ending per muscle fiber, but at birth several active motor nerve endings converge to a common endplate (Redfern 1970). All of them except one are subsequently eliminated and the state of activity of the neuromuscular junction plays a decisive role in this elimination (Benoit & Changeux, 1975, 1978). This epigenetic step results in the formation of the motor units which work together to coordinate the contraction of the whole muscle (Buchtal & Schmalbruch 1980).

In the cerebellar cortex, similarly, the interactions between parallel fiber and climbing fiber synapses on Purkinje cells reveal heterosynaptic competition during development. The mature monoinnervation of Purkinje cells) by their climbing fibre, afferents from the inferior olivary nucleus is preceded by a transient stage of multiple innervation (Mariani & Changeux 1980). In the rat, synapse exhuberance reaches a maximum of up to 5 climbing fibers per Purkinje cell (about 3.5 on average) on postnatal day 5 and then regressing until monoinnervation is established on postnatal day 14-15. Granule cell precursors suppression by postnatal X-irradiation indicate that granular cells are not involved in the early part of climbing fiber synapse elimination but only the final phase, after postnatal day 8, would be driven by parallel fibers activity (Lohof et al, 1996). Genetic mutations have also been shown to alter synaptic epigenesis in the mouse (Changeux & Mikoshiba 1978).

The innervation of the sympathetic sub-mandibular ganglion cells undergoes profound reorganization during postnatal development leaving individual ganglion cells in the adult innervated by many-fold fewer axons than they were at birth (Lichtman, 1977, 1980; Sheu et al., 2017).

These and many other studies (Luo & O'Leary, 2005; Ko et al., 2011; Kano & Hashimoto, 2012; Li et al., 2017; Bailly et al, 2018) have shown that,

when neuronal activity is artificially modified, synaptic elimination is altered. At variance with the "Lamarckist-constructivist" scheme (Quartz & Sejnowski, 1997), blocking the activity maintains a high number of connections. Activity thus enhances synaptic elimination. As I have said in the past « to learn is to eliminate » (Changeux, 1983, 1985). Many groups (Shatz, Lichtman and others) have since abundantly documented this. Extending this idea to postnatal cognitive development itself (from object permanence in infants to logical reasoning in adolescents and adults), Olivier Houdé said, "to develop is to inhibit" (Houdé, 2000, 2019).

The classical information-processing scheme of the nervous system is based on the notion that its internal states of activity directly result from interactions with the outside world. In fact, from very early on, there is intense spontaneous electrical and chemical activity within the nervous system of the embryo and of the fetus (Hamburger, 1970; Ripley & Provine, 1972). Chick embryos move within the egg as early as 2 days of incubation. These spontaneous movements are blocked by curare (Levi Montalcini, 1936, see 2000) and coincide with electrical activity of the same frequency arising in spinal cord neurons. In the human, these movements start during the eighth week of embryonic development, continue, and diversify during the following months. Such spontaneous activity develops in a strictly endogenous manner and results from molecular oscillators consisting of slow and fast ionic channels (Berridge & Rapp, 1979). The cost of this activity in terms of structural genes is very small and bears no relation to its enormous potential for interaction and combination, which results from the activity's eventual contribution to the epigenesis of neuronal synaptic networks. In the retina, the spontaneous activity of the ganglion cells (Galli & Maffei, 1988) forms correlated patterns, or waves (Maffei & Galli-Resta, 1990, confirmed by Meister et al 1991; Shatz, 1996).

The mechanism of wave initiation and propagation is not fully understood yet it involves synaptic transmission mediated by nicotinic acetylcholine receptors (nAChRs) (Feller et al., 1996; Penn et al., 1998). These waves of endogenous retinal activity are shown to play an important role in the epigenesis of neural networks through selective synapse

stabilization. In mice deprived of the high-affinity nAChR beta2 subunit (Picciotto et al., 1995, 1998; Zoli et al., 1998), the pattern of retinogeniculate and retinocollicular projections was found to be altered (Rossi et al, 2001). In contrast, although alpha 4 subunit is the predominant partner of the beta 2 subunit in the formation of brain high affinity nAChRs, its deletion did not cause defects in retinofugal segregation. The initial developmental phase of retinal projections looked normal in beta 2 mice until postnatal day 4. This result, together with previous observations showing that the anatomy and the spatial resolution of the retina were normal in beta 2 mice, indicate that the deficit observed at later ages is not due to defects in retinal ganglion cells, programmed cell death or path finding errors of optical nerve fibers, but to the aberrant segregation of ipsilateral and contralateral axons at the target level. Consistent with these data, the beta-2 deleted mice show an expansion of the binocular subfield of the primary visual cortex and a decrease in visual acuity at the cortical level but not in the retina. The nAChR beta 2 subunit is thus necessary for the developmental epigenesis of the visual system at both anatomical and physiological levels (Rossi et al, 2001; Grubb et al, 2003).

The example of the visual system may plausibly be extended to other sensory motor systems and to a broader framework of a formal architecture of thalamocortical areas, in which top-down activity generated in hierarchically higher cortical areas plays a key role. Multiple nested “waves” of synaptic epigenesis take place during the postnatal development of the adult brain. As a consequence, a net decline of the total envelope of synaptic connections, which themselves sum up this laminated development, is observed (Huttenlocher & Dabholkar, 1997). In the primary visual cortex, for example, after a burst of synapse formation between age 3 and 4 months, synaptic density reaches its peak at 140–150% of adult levels between the ages of 4 and 12 months, after which the mean number of synapses per neuron declines (Huttenlocher, 1990).The decline observed during late childhood plausibly reflects the underlying rich nesting of selection steps in a cascade of critical periods that proceeds far beyond puberty. In rats, the maximum synaptic density is reached within a few weeks after birth, whereas in humans it takes over three years (Bourgeois,

1997). Moreover, rats show little loss of synapses after maximum density is reached. On the other hand, in humans there is a steady decline until the total number stabilizes about the time of puberty (Huttenlocher & Dabholkar, 1997; Bourgeois, 1997; Petanjek et al., 2011), reflecting the initial exuberance and later pruning of connections. In contemporary humans, the process of synaptic refinement goes far beyond puberty: learning is lifelong (Petanjek et al., 2011). 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. Cat and monkey show intermediate stages of this process as life span and infant dependency increases. This major distinction between lower mammals and humans has to be borne in mind to understand the evolutive process of brain humanization. This places severe limitations in using lower mammals as models for human psychiatric and neurological conditions.

6. **Epigenesis of higher brain functions and global integration**

Among the cortical connections established in postnatal life are the long-range tracts between the frontal areas (Fuster, 2015) and other brain cortical areas (including sensory ones) (Goldman-Rakic, 1988, 1999; Hagmann et al., 2008; Collin & van den Heuvel, 2013; de Lange et al., 2019). Some years ago, the "global neuronal workspace" hypothesis was suggested, according to which these long-range connections primarily between prefrontal, parieto-temporal and cingulate cortices yield subjective conscious experience (Dehaene et al., 1998; Dehaene & Changeux, 2011) by broadcasting signals to multiple brain areas, thus allowing sensory inputs – such as seeing, hearing – conscious access to a whole brain "global workspace" (Baars, 1989).

Long-range connections, mostly originate from the pyramidal neurons in cortical layers II and III, are particularly abundant in the prefrontal cortex (von Economo & Koskinas, 1925), and form white matter bundles several of which originate from the prefrontal areas (Dejerine, 1895; Pugliese et al., 2009). Particularly important are these connections involved in planning, decision making, thought and socialisation, which have evolved

most dramatically between mice and humans (see Dehaene and Changeux 2011; Houdé, 2000, 2019).

The ontogeny and postnatal development of long-range connectivity expectedly reveal phases of exuberance and phases of selection and axonal pruning (Collin & van den Heuvel, 2013). Around birth, all major white matter tracts appear to be in place (Dubois et al., 2006; Hermoye et al., 2006), with at birth an over-representation of long-range connectivity followed rapidly by a decrease on the macroscopic scale. In nonhuman primates, a staggering 70% of callosal connections are eliminated (Innocenti & Price, 2005; LaMantia & Rakic, 1990). In human newborns, the evolution is slower. It has been suggested that the phase of exuberant axonal removal at the age of 2 years is completed accompanied by increasing information processing and cognitive – in particular language - development together with the "theory of mind" acquisition (Collin & van den Heuvel, 2013). The evolution continues during adolescence until adulthood with decreasing segregation and increasing integration mainly driven by modulation of connections stability and strength (Hagmann et al., 2010). It is expected to have major consequences on the laying down of cultural inprints, including the "epigenetic rules" associated with socialisation.

One essential aspect of postnatal development in the human brain is the epigenesis of long-range connections establishment (Huttenlocher & Dabholkar, 1997) between different cortical areas, especially those of the GNW linking the parieto-temporal-cingulate cortices with the prefrontal lobes, which are the centers for decision-making, rational thinking and social interaction. It is expected that these different areas develop rather independently (as for instance the visual areas for each eye) but need a strong synapse selection step to integrate them into a unique gobal workspace at the scale of the individual (as an integrated binocular vision in the visual system).

One question currently asked then is whether these long-range connections are especially vulnerable to some pathologies (Wei et al., 2019).

For instance, the onset of schizophrenia has been linked to susceptibility genes coding for several proteins involved in synaptic selection or pruning such as ERBB4, SLC1A3, RAPGEF4 and CIT28; the last is also involved in bipolar disorder (Karlsgodt et al., 2008). Links with NEUREXIN 1, which is involved in synapse formation and stabilization, have been reported (Cook & Scherer, 2008). Also, various mutations linked to autism are in genes that are involved in synapse formation and stabilization such as NEUROLIGINS 3/4, NEUREXIN 1 and SHANK 3, which code for synaptic adhesion and stability proteins (Bourgeron, 2009; Huguet et al., 2016). 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). In addition, increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning has been observed (Sellgren et al., 2019). A particular vulnerability of long-range connections 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 or autistic phenotypes as distinct from the mental retardation expected from global deficits in synaptogenesis.

One way this vulnerability was tested was to compare the dendritic branching of pyramidal neurons in wild-type mice and mutant mice, mentioned above, which lack the beta 2-subunit of the nAChR (Ballesteros-Yáñez et al., 2010). Loss of this subunit prevents the high-affinity binding of the neurotransmitter acetylcholine and, therefore, mice lacking the beta 2-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 these mice might possibly be showing an alteration in elementary conscious access (Avale et al., 2011; Koukouli et al., 2017).

These studies on mice may be relevant to a possible effect of chronic nicotine use on long-range connectivity. In humans, diffusion tensor

imaging (DTI), which allows the measurement 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 (Changeux & Lou, 2011; Kangiser et al., 2019). 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 (Changeux, 2010). Thus, there is support for an epigenetic control of the global neuronal workspace connectivity 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, to the extent that addicts may lose some conscious self-control of their actions (Joutsa et al., 2011; Changeux & Lou, 2011; Rømer-Thomsen et al., 2013). These obervations strengthen the still hypothetical conclusion that the epigenesis of long-range connections plays a critical role in elementary conscious access.

7. **Social and cultural imprints**

The extension of the postnatal 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. Among the many manifestations of cultural evolution, writing and reading appear as recent inventions. 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. Writing and reading is a recent cultural invention that evolved into distinct sub-systems and puts considerable demands to our cognitive system. The acquisition of reading and writing may be viewed as a typical example of epigenetically led down “cultural circuits”.

Historically, the first evidence for specialized writing and reading circuits in the brain was the discovery by the French neurologist Dejerine

(1914) of pure alexia, also known as alexia without agraphia. Individuals with pure alexia suffer from severe reading problems while other language-related skills such as naming, oral repetition, auditory comprehension or writing are typically intact. Alexia results from cerebral lesions in circumscribed brain regions including the supramarginal and angular gyri. New specialized sets of connections have been selected and consolidated as a consequence of written language learning. 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 positron-emission tomography (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). These conclusions have been consolidated and further expanded with functional magnetic resonance imaging (fMRI) scans from illiterate and literate groups (Dehaene et al., 2010). Acquisition of reading and writing may be viewed as an example of epigenetically laid down "cultural circuits" following epigenetic appropriation of fast developing connections around 5-6 years of age. It operates at a time of still very rapid synaptogenesis and persists into adulthood (Dehaene et al. 2010).

Interestingly, occidental alphabetic writing systems, recruits circuits which differ in part from those mobilized by the Chinese ideographic systems. In French readers readin French, activations were enhanced in left-hemisphere visual area V1, with the strongest differences between French words and their controls found at the central and horizontal meridian representations. In contrast, Chinese readers reading Chinese

showed enhanced activations in intermediate visual areas V3v/hV4, absent in French participants (Szwed et al., 2014).

Written language learning is but one of many social and cultural imprints acquired during the human brain's development. Cognitive development *per se*, i.e. acquisition of *object* unit and permanence in infants, then *number*, *categorization* and *reasoning* operations in children and adolescents, depend both on brain inner regulation processes and socio-cultural imprints (Houdé, 2000, 2019). Thus, the adult human brain connectivity may be viewed as a complex intertwining of cognitive, social and cultural circuits epigenetically laid down during development within the framework of a human-specific genetic envelope. Important bridges could then be established between the gene expression level and the highest level of the interaction of the brain with its social and cultural environment.

8. **Conclusion: the habitus of the human subject**

Even if advocated by such a distinguished scholar as Piaget (1976), there is no compelling evidence whatsoever that the culturally acquired phenotypes may sooner or later become genetically transmitted. They have to be learned at each generation from adults to children and epigenetically transmitted from generation to generation, starting even in the womb of the mother, until the adult stage. Teaching reading and writing in 5-6-year-old children requires elaborate pedagogic strategies which in a general manner are absent in non-human primates (Premack, 2007).

As a major consequence, the acquisition of skills and practices associated with the symbolic experience and emotional labelling characteristic of rational thinking (science), rules of conduct (ethics), and shared feelings (art) become stably internalized epigentically in the connectivity of the brain and become exclusive of others. Their "forgetting" is considerably slower than their speed of acquisition through synapse stabilisation processes. They contribute to what Bourdieu refers to as the 'habitus' of the subject: internalized routine modes of perception, action, and evaluation, which often last a lifetime (Changeux, 2006). Possibly, since the domestication of fire, the grouping of human individuals into stable,

autonomous and geographically dispersed societies has led to the differentiation and divergence of cultures between human groups with separate languages, knowledge backgrounds, techniques and, most of all, systems of beliefs, thus raising cultural fences. These fences, as already noted by Levi Strauss (1952), are such that, because of its different culture, "the other" may no longer be regarded as a human being. A "dehumanization" process frequently accompanies the diversification of cultures (Changeux, 2018, 2019). Most often, a widespread "ethnocentrism" of the subject takes place, where he/she considers his/her own culture as "The only One Culture" existing on earth. Such cultural habitus acquired in the child and "printed" in its brain remains stable for years or even decades. It manifests itself, for instance, in the accent in spoken language. It can only be fully renewed with the re-learning step that takes place with the next generation (Changeux, 2018, 2019).

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 and written language and, perhaps even more significantly, artistic activity 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. More important for my thesis, language, writing, and cognitive development in general (about objects, numbers, categorizations, and reasonings or decision-makings) rely on epigenetic cultural transmission framed within a robust human-specific 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 & Dabholkar, 1997; Bourgeois, 1997) – offers the developing brain the opportunity for intense self-regulations and social and cultural interactions.

From a neuroscientific perspective, ethical and social norms may therefore be conceived as spatiotemporal patterns of neuronal activity that can be mobilized within the "conscious neuronal workspace" and stored as long-term traces in brain memory (Evers & Changeux, 2016; Farisco et al.,

2018; Changeux, 2018). In more general terms, the prefrontal region of the cerebral cortex acts as a "temporal buffer" between past events and future actions and contributes to decision-making within the context of the individual's history. In such a neuronal workspace, "neurally encoded rules" associate a context with a specific behavioral response in a top-down manner. This is referred to as cognitive control (Houdé, 2019) and coordinates thoughts or actions in relation to internal goals. Brain imaging fMRI revealed a hierarchical cascade of executive processes, which are implemented in distinct regions, from posterior premotor to rostral lateral prefrontal cortex, typically Brodman's area 46 (Houdé et al, 2000, 2011; Houdé & Tzourio-Mazoyer, 2003; Koechlin, 2016). Behavioral rules are sorted at these nested levels of information processing, the highest-level ones controlling the underlying ones closer to the senses. This scheme may be extended assuming that ethical or social norms control rules and part of the "concurrent behavioral strategies" in decision-making (Evers & Changeux, 2016). From birth on, and possibly even prenatally, the baby is exposed to a social and cultural environment. During its development, an epigenetic selection of neuronal networks accompanies the acquisition of the ethical rules of the social community to which the child and her/his family belong. These ethical rules are often linked with symbolic representations of the cultural community, and the acquisition of such ethical rules and symbolic systems has been compared to language acquisition. Yet, to justify such cultural differences, written language, holy books, moral rules, sexual practices, food or clothing rituals among others are evoked as irreducible transcendentals even more fundamental than political or economical differences. The universe of cultural differences and thus of potential conflicts is immense. How to face this dramatic situation? How to overcome the cultural epigenetic fences that plague our planet?

One possibility to consider is to make an effort to gain some distance with respect to the emotions mobilized by what is believed to be a "transcendental" act of faith. This might be achieved, at the individual level, through the understanding that such belief is simply an acquired cultural trait invented and epigenetically perpetuated by the brains of humans in society to consolidate their social bond. Following Durkheim, such social

facts would possess an objective reality that could be "studied like a physicist studies the physical world," taking into account the fact that they are produced and propagated in a steadily evolving socio-historic context. Within this context, the possibility of developing in the brain new ethical rules of "good life with and for the other" in just institutions (Changeux & Ricoeur, 2000) or "epigenetic proaction" has been proposed (Evers & Changeux, 2016). Another possibility, advocated by Levi-Strauss, is to look for a "coalition of cultures" which let build up cumulative series. Such a coalition would favour the evolution of cultures supporting progress and cooperation rather than exclusion resulting in the breakdown of the cultural fences.

Last, a possibility – seemingly easier to achieve – is to be found in education. Cultural differences are infused into the child brain already at birth (possibly even before for language), in the family environment, and consolidated by the schooling system. Secular education is a system of public education, where conspicuous symbolic (religious or philosophical) systems as well as the biased unilateral presentation of the diversity of symbolic systems have been banned. Still it has been recognized as one of the best systems in the world to learn and practice tolerance and respect for cultural differences (Evers & Changeux 2016; Changeux, 2018).

In conclusion, we are neurobiologically predisposed toward specific values, such as self-interest, empathy, sociality, and so on, and our brain structures develop in response to ethical and social norms in our cultural and social context. Given the long-lasting plasticity of our brains and the underlying synaptic epigenesis mechanisms involved, we may influence, both biologically and culturally, how the brain responds to and constructs new norms with the aim to account for a harmonious future of humanity in our fast evolving planet.

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