Can We Be Epigenetically Proactive?

Kathinka Evers

The human brain is an essentially evaluative organ endowed with reward systems engaged in learning and memory as well as in higher evaluative tendencies. Our innate species-specific, neuronally-based identity disposes us to develop universal evaluative tendencies, such as self-interest, control-orientation, dissociation, selective sympathy, empathy, and xenophobia. The combination of these tendencies may place us in a predicament. Our neuronal identity makes us social, but also individualistic and self-projective, with an emotional and intellectual engagement that is far more narrowly focused in space and time than the effects of our actions. However, synaptic epigenesis theories of cultural and social imprinting on our brain architecture suggest that there is a possibility of culturally influencing these predispositions. In an analysis of epigenesis by selective stabilisation of synapses, I discuss the relationships between genotype and brain phenotype: the paradox of non-linear evolution between genome and brain complexity; the selection of cultural circuits in the brain during development; and the genesis and epigenetic transmission of cultural imprints. I proceed to discuss the combinatorial explosion of brain representations, and the channelling of behaviour through "epigenetic rules" and top-down control of decision-making. In neurobiological terms, these "rules" are viewed as acquired patterns of connections (scaffoldings), hypothetically stored in frontal cortex long-term memory, which frame the genesis of novel representations and regulate decision-making in a top-down manner. Against that background I propose the possibility of being epigenetically proactive, and adapting our social structures, in both the short and the long term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of our brains.

Keywords
Cultural circuits | Empathetic xenophobia | Epigenetic proaction | Epigenetic rules | Neuroethics | Precaution | Responsibility | Selective sympathy | Species-specific identity | Synaptic epigenesis

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1 Introduction

Contemporary neuroscience no longer views the brain as an input-output processing device but as an autonomously active, self-referential, and selectional system operating in a projective style, which is in constant social interaction and in which values are incorporated as necessary constraints. The idea that evolution by natural selection has given rise to an essentially evaluative cerebral architecture raises the question whether, in the human species, such neurobiologically-based predispositions have further developed the means to generate novel specific values on higher cognitive levels. The concept of "value" would then play a central role as something that is taken into account in decision-making and that influences a choice, selection, or decision, that can occur on many levels—non-conscious as well as conscious—as a basic biological function or as a feature of advanced moral reasoning. But, if we are born evaluators, to what extent can these predispositions with which we are all born be culturally controlled?

In this article, I suggest that our innate species-specific neurally based identity disposes us to develop universal evaluative tendencies, such as self-interest, control-orientation, dissociation, selective sympathy, empathy, and xenophobia. The combination of these tendencies may place us in a practical and moral predicament. Our neuronal identity as persons makes

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us social, but also individualistic and self-projective, with an emotional and intellectual engagement that is far more narrowly focused in space and time than the effects of our actions.

However, the neuronal organisation of our adult brain develops in the course of a fifteen year-long period following birth, during which, and, to a lesser extent, after which it is subject to cultural influence, both on the individual level and, at the social group level, across generations (Lagercrantz 2005; Lagercrantz et al. 2010; Collin & van den Heuvel 2013). Synaptic epigenesis theories of cultural and social imprinting on our brain architecture (which differ from less discriminative epigenetic modifications of nuclear chromatin) (Changeux 1985; Kitayama & Uskul 2011) suggest that there is an interesting possibility, which, in my opinion, has hitherto been underestimated. That is, we could potentially be *epigenetically proactive* (Evers 2009) and adapt our social structures, in both the short and the long term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of our brains.

2 The social individualist

2.1 An egocentric evaluator

The human brain is intrinsically active: it produces electrical and chemical activity both in response to external stimuli and, spontaneously, independently of them. The brain is an autonomously-active motivated neuronal system, genetically equipped with a predisposition to explore the world and to classify what it finds there (Changeux 1985, 2004). On-going spontaneous activity is present throughout the nervous system. In the embryo, spontaneous movements (Narayanan & Hamburger 1971) and waves of endogenous retinal activity (Galli & Maffei 1988; Goodman & Shatz 1993) are thought to play an important role in the epigenesis of neural networks through synapse selection (see below). On-going spontaneous activity is also present in the adult brain, where it is responsible for the highly variable patterns of the electroencephalogram(EEG; Berger 1929; Raichle et al. 2001). Thalamocortical networks generate a variety of oscillations, whose rhythms change across the sleep-wake cycle (Llinas & Paré 1991). Optical imaging methods in anesthetized animals also reveal fast spontaneous states of neuronal activity that, far from being random, exhibit patterns that resemble those evoked by external stimuli. In parallel, functional neuroimaging studies in humans have shown a globally-elevated brain metabolism at rest, with localized patterns suggesting that particular cortical regions are maintained in a high, although variable, state of activity referred to as "default mode" by Raichle et al. (2001).

Hypotheses of knowledge acquisition posit that patterns of spontaneous activity, referred to as "pre-representations", arise in the brain and are selected by reward signals as "representations" confirmed by both external experience and internal processes of evaluation within a conscious neuronal workspace (Dehaene & Changeux 2011). Such "models of the world" are stabilised through "cognitive games" by analogy with Wittgenstein "language games", as permanent features of the developing cognitive apparatus, according to a process referred to as "mental Darwinism" (Changeux 2004).

Anticipation of reward signals introduces a delay between the elaboration of tacit plans of action and actual interaction with the world performed by the organism, which presupposes a distinction of temporal states: awareness of the present, remembrance of the past, and anticipation of the future (Barto & Sutton 1982; Schultz et al. 1997; Dehaene & Changeux 2000; Schultz 2006). Without any capacity to evaluate stimuli, the brain could neither learn nor remember: it has to prefer some stimuli to others in order to learn. This classical idea in learning theory has been expressed in neuronal terms by Dehaene & Changeux (1991), and by Edelman in his accounts of primary consciousness (Edelman 1992). In these accounts, learning is a change in actual behaviour, or the storage of a trace subsequently unveiled (Dudai 1989, 2002) through brain categorizations of stimuli. These are given in terms of positive or negative values, understood as something that is taken into account in decision-making and that influences a choice, selection or decision, which can occur on many levels. Through its intense and spontaneous activity, the brain has also been described as a narrative organ, spinning its own neuronal tale (Evers 2009). The narrations will vary greatly between individuals, but each will be self-projective.

The natural egocentricity or individualism of the human brain appears quite pronounced. In its projection of autonomously-produced images, the brain refers all experiences to itself, that is, to its own individual perspective. This self-projection is a biological predisposition that humans possess innately and that is closely connected to our predisposition for developing self-awareness, which Edelman suggests is a necessary condition for developing higher-order consciousness (Edelman 1992; Denton 2006; see also Tulving 1983). The existence of a self-projecting systems monitoring internal processes in the brain was suggested by an early Positron Emission Tomography (PET) study of self-generated actions showing hemodynamic activity in the posterior cingulate cortex (Blakemore et al. 1998). This observation was confirmed and extended by magneto-encephalography following synchronization in the gamma range (55–100 Hz), thus defining a major network of the brain: the paralimbic interaction between the medial prefrontal/anterior cingulate and medial parietal/posterior cingulate cortices and subcortical regions (Lou et al. 2004; rev. Changeux & Lou 2011). Damasio (1999) distinguished a “core consciousness” (core self) from an “extended consciousness” (extended self) that we consider as analogous to the “minimal self” and “extended self” of Gallagher (2000). Minimal self-awareness is prereflexive, immediate and normally reliable, while still involving a sense of ownership of experience (Gallagher 2000). The “extended self” is a coherent self that persists across time and requires a system that can retrieve long-term memories of personal experiences—namely, episodic memory (Gardiner 2001). Consequently, episodic memory retrieval becomes an indispensable component of the more complex forms of self-awareness and consciousness (Tulving 1983).

In the course of growing up, the infant develops the capacity to focus its attention; it learns to distinguish between and recognise objects in its environment, such as faces, and becomes aware of itself as standing in various relations to these objects. Conscious processing develops into auto-distinction (when “this-here” is distinguished from “that-there”). When further developed, the individual becomes aware of itself as a subject of experience and ascribes mental states to itself: auto-distinction evolves into self-awareness (when “this-here” becomes “I”) usually at around one and a half years of age (Lagercrantz 2005), and possibly even earlier (Falck-Ytter et al. 2006; see also Rochat 2001). From the age of six to twelve months, the child typically sees a “sociable playmate” in the mirror’s reflection. Self-admiring and embarrassment usually begin at twelve months, and at fourteen to twenty months most children demonstrate avoidance behaviours. Finally, at eighteen months 50% of children recognize the reflection in the mirror as their own and by twenty to twenty-four months this rises to 65%—this is revealed, for instance, by them trying to evince marks on their own nose, taking advantage, in all these instances, of their episodic memory abilities (see Tulving 1983).

An evolved survival function that adds an evaluative element to our brain’s self-projective mode of operation is self-interest, expressed as a desire to survive, to be well-fed, safe, to reproduce, and so on. This is not a defining characteristic, for there are exceptions, for example subjects who have a very poorly developed self-interest (Damasio 1994; Damasio & Carvalho 2013). Nor is it necessarily rational, since biological evolution is circumstantial. There is an abundant literature on the phenomenologically rich concept of self-interest in philosophy and ethics, in terms e.g., of enlightenment, egoism, capacity for altruism, etc. Such issues are relevant and interesting but beyond the scope of this discussion. In the present context, self-interest is understood in a minimalistic sense, as an evolved survival function that adds an evaluative element to our brain’s self-projective mode of operation.

Self-interest is also a source of the urge to control the immediate environment, and of the need for familiarity, security, and preference for the known. The subjective experience of some level of control and the security that this provides is in fact a necessary condition for the individual to develop in a healthy manner and to consolidate an integrated sense of self (Ledoux 1998). When the external circumstances become severely disturbing, we feel increasingly threatened and have a defence mechanism that is eventually activated: *dissociation*, here understood as a process whereby information—incoming, stored, or outgoing—is actively prevented from integration with its usual or expected associations.

The human being is, in this sense, a "dissociative animal": we spend a considerable amount of intellectual and emotional energy on distancing ourselves from a wide range of things that we consciously or non-consciously fear or dislike (Evers 2009). When an experience is too painful to accept, we sometimes deliberately do not accept it; instead of integrating it into our ordinary system of associations, we push it away from us, and prevent it from being integrated into our consciousness. Pushed to an extreme, this tendency may become pathological, e.g., in the development of Dissociative Identity Disorder (cf. DSM-IV), but as a non-pathological process it is an important adaptive function, and a valuable evolutionary asset allowing us to survive events that we would otherwise be unable to endure (Putnam 1989; Evers 2001).

So far, I have described the brain as an autonomously active, self-projective, and selectional neural system with innate evaluative tendencies, e.g., self-interest, control-orientation, and dissociation. These cerebral features characterize the individual, but they are also reflected in the social relationships proper to the human species.

2.2 Selective sympathy & empathetic xenophobia

In social animals, self-interest is a source of interest in others. In the case of humans, this social interest focuses primarily on those to whom the self can relate and with whom it identifies, such as the next of kin, the clan, the community, etc. The human brain conjugates opposite tendencies: first, embodied in the human subject, it is engaged in highly individualistic and self-projective actions, such as the search for water or food. But it also mediates co-operative social relationships: the "I" is extended to endorse the group, as a "we", and distinctions are drawn between "us" and "them" (Ricoeur 1992; Changeux & Ricoeur 2000). Sympathy and aid is typically extended to others in proportion to their closeness to us in terms of biology, e.g., face recognition (Michel et al. 2006; Hills & Lewis 2006), racial out-group versus in-group distinctions (Hart et al. 2000; Phelps et al. 2003), culture, ideology, etc.

Imagining an action or actually performing that action both have similar neural circuits (which include the premotor cortex, supplementary motor area, cerebellum, parietal cortex, and basal ganglia) to those activated when one observes, imitates, or imagines actions performed by other individuals (Jeannerod 2006; Decety 2012). The model mechanism suggested is that actions are coded in terms of perceivable effects (Hommel et al. 2001). Performing a movement leaves a memory of the association between the motor pattern by which it was generated and the sensory effects that it produces. Such stored associations can then be used to retrieve a movement by anticipating its effects. This perception-action coupling mechanism, which includes active sensing and motor-sensory loops (Gordon & Ahissar 2012) and to which may be added the motor theory of language (Liberman & Mattingly 1985), offers a mechanism for intersubjective communication and social understanding by creating functional links between first-person and third-person information (Decety & Sommerville 2003; Jackson & Decety 2004).

Functional Magnetic Resonance Imaging and magneto-encephalography among other methods have led to the demonstration that when children or adults watch other subjects in pain, the neural circuits mobilized by the processing of first-hand experience of pain are activated in the observer (Singer et al. 2004; Cheng et al. 2008). This sharing allows mapping of the perceived affective cues of others onto the behaviours and experiences of the self-oriented response. Decety (2012) argues that, depending on the extent of the overlap in the pain matrix, and complex interactions with personal dispositions, motivation, contextual information, and self-regulation, this can lead to personal distress (i.e., self-centred motivation) or to empathic concern (i.e., an other-oriented response). This basic somatic sensorimotor resonance plays a critical role in the recognition and sharing of others' affective states.

There is an important neural distinction between apprehending and caring that makes it possible to understand the affective state of another without feeling engaged in it. Studies in the neurobiology of empathy (here understood as the ability to apprehend the mental states of others), and sympathy (the ability to care about others) suggest that these abilities involve complex cognitive functions with large individual and contextual variations that depend on both biological and socio-cultural factors (Jackson & Decety 2004; Singer et al. 2004; Singer et al. 2006; Iacoboni et al. 2005; Jackson et al. 2006; Lawrence et al. 2006; Parr & Waller 2006; Engen & Singer 2013). Such results are important, because appreciating the brain's role in apprehending and responding to the affective states of others can help us understand people who exhibit social cognitive disorders and are deficient in experiencing socially relevant emotions such as sympathy, shame, or guilt.

However, even in supposedly healthy human brains the capacity for other-oriented responses, such as sympathy, is pronouncedly selective and limited by spontaneous aggressive tendencies (Panksepp 1998; Lorenz 1963). When sympathy and mutual aid is extended within a group, they are also (de facto) withheld from those that do not belong to this group. In other words, interest in others is ordinarily expressed positively or negatively towards specific groups—but very rarely are attitudes extended to universal coverage, for example as attitudes towards the entire human species, or towards all sentient beings.

Understanding does not entail compassion, but is frequently combined with emotional dissociation from "the other". We can easily understand, say, that a child in a distant country probably reacts to hunger or pain in a way that is similar to how children in our own country react to hunger or pain, but that does not mean that we care about those children in equal or even comparable measures. Indeed, if understanding entailed sympathy, the world would be a far more pleasant dwelling place for many of its inhabitants. By nature, we are "empathetic xenophobes" (Evers 2009): we are empathetic by virtue of our intelligence and capacity to apprehend the mental life of a relatively wide range of creatures, but far more sympathetic to the closer group into which are born or choose to join, remaining neutral or hostile to "out-group" individuals.[1]

Thus, in spite of our natural capacity for empathy, sympathy, and mutual assistance, the human being can also be described as a self-interested, control-oriented, dissociative xenophobe. In view of their historic prevalence, it is not unlikely that these features have evolved to become a part of our innate neurobiological identity and that any attempt to construe social structures (rules, conventions, contracts, etc.) opposing this identity must, in order to be realistically implemented, take this biological challenge into account in addition to the historically well-known political, social, and cultural challenges.

A major practical problem is that the effects of our actions are not limited, as are our capacities for engagement. The difficulty of wide involvement due to the brain's self-projective egocentricity is matched by a capacity to cause large-scale effects, which poses serious problems whenever large-scale or long-term solutions are needed—say, to improve the global environment, reduce global poverty, or safeguard future generations. Our societies are importantly construed around egocentric and short-term perspectives—political, economical, etc.—making it extremely difficult to put global or long-term thought and foresight into practice. This is of course only to be expected, since our brains'

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[1] I am here discussing social attitudes in terms of subjective evaluators, but they can also be discussed in terms of non-conscious non-feeling units. Some current neuroscience literature may prefer to discuss the issue not from the point of view of subjective definitions but rather from the perspective of relevance detection and evaluation that is objectively observed.

neuronal architectures are engaged in social interactions and determine the social structures that we can and do develop.

However, our brain identity incorporates social influence. Culture and nature stand in a relationship of mutual causal influence: whilst the organisation of our brains in part determines who we are and what types of societies we develop, our social structures also have a strong impact on the brain's organisation; notably, they impact upon cultural imprints epigenetically stored in our brains. The genetic control over the brain's development is subject to epigenetic evolutionary processes; that is to say, to a coordinated and organised neuronal development that is the result of learning and experience and that is intermixed with the action of genes. The door to being epigenetically proactive is, accordingly, opened. In the following analysis of epigenesis by selective stabilisation of synapses I shall discuss the relationship between genotype and brain phenotype; the paradox of non-linear evolution between genome and brain complexity; the selection of cultural circuits in the brain during development; and the genesis and epigenetic transmission of cultural imprints.

3 Neuronal epigenesis

3.1 Genotype & brain phenotype: The paradox of non-linear evolution between genome & brain complexity

The comparison between what we presently know about human genomes and the brain phenotype raises the paradox of a non-linear evolution between the complexity of the genome and that of the brain (Changeux 1985, 2012b). From a molecular neurobiologist's perspective, the cognitive abilities and skills required for the highest functions of the human brain are built from a cascade of events driven by a "genetic envelope", which makes the difference between *Homo sapiens* and the human family's earliest ancestors, but which cannot be simply related to genome size, nor to the number of genes.

The total amount of DNA housed in the haploid genome is approximately 3.1 billion base pairs, but no more than 20,000–25,000 gene sequences (1.2% of our genome code for exons—the DNA components of genes), and this number does not significantly differ from mouse to human. Moreover, the difference in full DNA sequences are very limited: between humans and chimpanzees they comprise no more than 4% of the genome. However, the total number of neurons in the human brain is in the order of 85 billion, compared to about 70 million in the brain of the mouse (Azevedo et al. 2009). Yet, notwithstanding the increase in cell numbers, with each neuron possessing its particular connectivity and its set of genes expressed, mammalian brain anatomy has evolved dramatically from a poorly corticalized lissencephalic brain with about 10–20 identified cortical areas to a brain with a very high relative cortical surface, multiple gyri and sulci, and possibly as many as 100 identified cortical areas (Mountcastle 1998). Thus, there exists a remarkable nonlinear relationship between the evolution of brain anatomy and the evolution of the genome organisation.

Molecular and cellular explanations have been suggested to account for this nonlinear relationship. One is the combinatorial expression of spatio-temporal patterns of genes that affect development (Changeux 1985; Edelman 1987; Tsigelny et al. 2013). Another, non-exclusive explanation, is the contribution of "epigenetic mechanisms" driven by interaction with the environment in the course of the long postnatal period of brain maturation—circa 15 years in humans—during which critical and reciprocal relationships take place between the brain and its physical, social, and cultural environment. It is on these epigenetic mechanisms that I shall focus here.

3.2 The epigenesis of neuronal networks by selective stabilization of synapses

The word "epigenesis" can be traced back to William Harvey (1651), who stated in contrast to contemporary preformationist views that the embryo arises by "the addition of parts budding out from one another". It was subsequently used by Conrad Waddington (1942) to specify the relationship between the genes and their environment to produce a phenotype. This is also the meaning adopted in the theory of the epigenesis of neuronal networks by selective stabilization of synapses, according to which the environment affects the organisation of connections in an evolving neuronal network through the stabilization or elimination (pruning) of labile synapses, under the control of the state of activity of the network (Changeux et al. 1973). This meaning, which I shall use henceforth, contrasts with the more recent and biochemically distinct meaning of the word *epigenetic*, **which** refers to the status of DNA methylation and histone modification in a particular genomic region. This concerns the neuronal nucleus, but not the diversity of individual synaptic contacts (Sassone-Corsi & Christen 2012). The modulatory role of chromatin modifications in long-term memory has already been described (see e.g., Levenson & Sweatt 2005), but the informational content involved—which relies upon cell bodies—is expected to be in orders of magnitude smaller that of synaptic epigenesis, based upon the combinatorial power of individual synapses.

During embryonic and postnatal development, the million billion (10^{15}) synapses that form the human brain network do not assemble like the parts of a computer, that is, according to a plan that precisely defines the disposition of all the individual components. If this were the case, the slightest error in the instructions for carrying out this program could have catastrophic consequences. On the contrary, the mechanism appears to rely on the progressive setting of robust interneuronal connections through trial-and-error mechanisms that formally resemble an evolutionary process by variation selection (Changeux et al. 1973; Changeux & Danchin 1976; Edelman 1987; Changeux 2012a). At sensitive periods of brain development, the phenotypic variability of nerve cell distribution and position, as well as the exuberant spreading and the multiple figures of transiently-formed connections originating from the erratic wandering of growth cone behaviour, introduce a maximal diversity of synaptic connections. This variability is then reduced by the selective stabilization of some of the labile contacts and the elimination (or retraction) of others. The crucial hypothesis of the model is that the evolution of the connective state of each synaptic contact is governed globally, and within a given time window, by the overall "message" of signals experienced by the cell on which it terminates (Changeux et al. 1973).

One consequence of this is that particular electrical and chemical spatiotemporal patterns of activity in developing neuronal networks are liable to be inscribed under the form of defined and stable topologies of connections within the frame of the genetic envelope. In humans, about half of all adult connections are formed after birth at a very fast rate. The nesting of these multiple traces directly contributes to forming and shaping the micro- and macroscopic architecture of the wiring network of the adult human brain, thus bringing an additional explanation to the above-mentioned non-linearity paradox.

Another consequence of the synapse-selection model (originally presented as a "theorem of variability") is that the selection of networks with different connective topologies can lead to the same input-output behavioural relationship (Changeux et al. 1973). This accounts for an important feature of the human brain: the constancy or "invariance" of defined states of behaviour, despite the epigenetic "variability" between individual brains' connectivity.

Finally, both the spontaneous and the evoked activity may contribute to synapse selection. In this framework, a suggestion has been made that reward signals received from the environment may control the developmental evolution of connectivity (Gisiger et al. 2005; Gisiger & Kerszberg 2006). In other words, reinforcement learning would modulate the epigenesis of the network. The model has been implemented in a case of the learning of a visual delayed-matching-to-sample task (see below). This process of synaptic selection by reward signals may concern the evolution of brain connectivity in single individuals, but it also concerns the exchange of information and shared emotions or rewards between individuals in the social group (Changeux 1985, 2004; Gisiger et al. 2005). This is an important part of our argument; it may thus play a critical role in social and cultural evolution.

3.3 The selection of cultural circuits in the brain during development & the epigenetic transmission of cultural imprints

There is an abundance of experimental studies that are consistent with, or directly support, the model of synapse selection. In humans the maximum synaptic density is reached within three years, then steadily declines until the total number stabilises around the time of puberty (Huttenlocher et al. 1997; Bourgeois 1997; Petanjek et al. 2011). Yet the process of synaptic refinement goes far beyond puberty: learning is life-long (Petanjek et al. 2011). The observed global decline in synaptic numbers during childhood plausibly reflects a rich cascade of elementary steps of learning by selection. Numerous studies have shown that when neuronal activity is experimentally modified, synaptic elimination is altered (Benoit & Changeux 1975, 1978; Stretavan et al. 1988; Purves & Lichtman 1980; Luo & O'Leary 2005; Innocenti & Price 2005; Collin & van den Heuvel 2013). At variance with the classical Lamarckist-constructivist scheme (Quartz & Sejnowski 1997), blocking the activity maintains a high number of connections: it is activity that enhances synaptic elimination (Benoit & Changeux 1975, 1978; Stretavan et al. 1988; Luo & O'Leary 2005). Thus "to learn is to eliminate" (Changeux 1985).

Among the cortical connections established in post-natal life are the long-range tracts between the frontal areas (Miller & Cohen 2001; Fuster 2008) and other brain cortical areas (including sensory ones) (Goldman-Rakic 1987; Goldman-Rakic 1999; Hagmann et al. 2008; Collin & van den Heuvel 2013). Some years ago, it was suggested, according to the "global neuronal workspace" hypothesis, that these long-range connections, by broadcasting signals to multiple brain areas, yield subjective "conscious" experience by allowing sensory inputs—seeing, hearing and so on—global access to many brain areas (Dehaene et al. 1998; Dehaene & Changeux 2011). The long-range connections would provide a structural basis for the global experience known as conscious access.

These long-range connections are particularly important in the case of the prefrontal areas which contribute to planning, decision-making, thought, and socialisation. 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). In human newborns evolution is slow, and it has been suggested that the phase of exuberant long axon removal is largely completed at the age of two years, accompanied by increasing information processing and cognitive development (Collin & van den Heuvel 2013). Evolution continues during adolescence until adulthood with decreasing segregation and increasing integration, mainly but not exclusively driven by modulation of connections strength (local synaptic elimination persists in the adult; Petanjek et al. 2011). It is expected to have major consequences on the laying down of cultural imprints including the "epigenetic rules" associated with socialisation.

The acquisition of reading and writing may be viewed as a typical example of epigenetic development of "cultural circuits". Writing and reading are recent cultural inventions (about 5000 years old) that evolved into distinct sub-systems and put considerable demands on our cognitive system. Historically, the first evidence for specialized writing and reading circuits in the brain was the discovery by the French neurologist Dejerine (1895) 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 angular and supramarginal gyri. New specialized sets of connections are present exclusively in individuals that have learned written language and have been selected and consolidated in the course of development at sensitive periods (4–6 years) as a consequence of an intensive period of education.

The human brain did not evolve to learn to read, but possesses enough epigenetic variability in the course of its development (and also —though to a lesser extent—in the adult) to incorporate a cultural invention of this kind. During the acquisition of reading and writing by Western subjects, representations for visual forms of words progressively settle into the occipito-temporal cortex, recruiting a subset of functionally-appropriate object recognition regions in the temporo-parietal junction (Dehaene et al. 2010). The group of illiterate individuals is consistently more right-lateralized than their literate controls (Petersson et al. 2007). Interestingly, alphabetic writing systems recruit circuits that differ in part from those mobilized by the Chinese ideographic systems. In French readers reading 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, which was absent in French participants (Szwed et al. 2014). Also, the capacity to read sheet music is selectively altered in music-specific forms of alexia. Neuronal circuits specific to a given culture may thus become epigenetically established in the brains of social group members. Written language-learning is only one of the many cultural imprints acquired during the development of the human brain (Changeux 1985). For instance, cross-cultural differences between Asian and Western participants manifest themselves as differential increases of fMRI in the medial prefrontal cortex with reference to self-judgment (Zhu et al. 2007; Ray et al. 2010) and also to diverse brain recordings in mind reading (Kobayashi et al. 2007), holistic attention (Hedden et al. 2008), or facial photo recognition (Na & Kitayama 2011). The adult human brain thus builds up from a complex intertwining of cultural circuits progressively laid down during development within the framework of a human-specific genetic envelope.

There is no compelling evidence that culturally-acquired phenotypes will sooner or later be genetically transmitted. What the evidence does show is that they have to be learned by each generation, by children from adults, and epigenetically transmitted from generation to generation, beginning in the mother's womb and up until the adulthood. Teaching reading and writing to circa five-year-old children requires elaborate pedagogic strategies, which in a general manner are absent in non-human primates (Premack 2007).

In short, cultural imprints have a physical reality in the human brain. Cultural imprints have also been demonstrated in non-human brains, e.g., by Peter Marler's work on birds' song-learning (Marler 1970). Yet the importance of cultural imprints on behaviour are comparatively much more important in humans compared to non-humans, in particular due to the long postnatal period of brain maturation. They play a critical role in shaping the brain phenotype in relation with the social group, through oral and written language but also though diverse culture-specific habits, traditions, and symbolic systems, including the ethical and social norms embodied in the adult brain.

I shall now proceed to discuss issues raised by the combinatorial explosion of brain representations and the channelling of behaviour through *epigenetic rules* and top-down control of decision-making.

> epigenetic rules $=_{\mathrm{Df}}$ In neurobiological terms, these "rules" shall be viewed as acquired patterns of connections (scaffoldings), hypothetically stored in frontal cortex long-term memory. They frame the genesis of novel representations and regulate decision-making in a top-down manner.

4 "Epigenetic rules" and top-down control of decision-making

4.1 The hierarchical architecture of the brain

It has been suggested that ethical and social norms are, from a perspective in which the brain is central, ultimately encoded as spatiotemporal patterns of neuronal activity that can be mobilized within the conscious neuronal workspace (Dehaene & Changeux 2011). Yet from a neurobiological standpoint, this view hinges upon the classical issue of the combinatorial explosion raised by the immense network of almost a million billion (10^{15}) interconnected synapses of the human brain. The question that arises, then, is how the particular patterns of neuronal activity, which, for instance, encode defined actions or perceptual events and ultimately ethical rules, are selected within this gigantic neural network. In my view, the concept of a hierarchical organisation of the brain needs to be taken into consideration more closely.

Analysis of the neurological deficits caused by lesions discloses hierarchical and parallel neural architectures that help us understand higher brain functions (Shallice & Cooper 2011). Among these is the inhibition of automatic (or reflex) actions and the elaboration of goal-directed behaviours and their control. In the brain, an evolutionary-recent territory of cerebral cortex architecture, the lateral prefrontal cortex, has been shown to play a critical role in the temporal control of behaviour. It serves as a "temporal buffer" between past events and future actions, allowing behaviours that follow internal goals to occur (Fuster 2001; Goldman-Rakic 1987; Petrides 2005). Moreover, the lateral prefrontal cortex exerts top-down control of cognitive processes associated with hierarchically-lower regions distributed in more posterior territories on the basis of internal plans, goals, or what may be referred to as "rules" (Miller & Cohen 2001; Passingham 1993; Shallice 1988; Dehaene & Changeux 1991; Koechlin et al. 2003). It thus contributes to decision-making within the actual context of a given individual history and stored memories (Damasio 1994) and to "neurally encoded rules" that can associate a context with a specific behavioural response and the ability to generalize a rule in novel circumstances.

An early formal model of learning by selection according to a rule was devised in the Wisconsin Card Sorting Task, which is commonly used as a test of the integrity of frontal lobe functions (Dehaene & Changeux 1991). It requires subjects to infer a "rule" according to which a deck of cards must be sorted, i.e., colour, shape, or number. Feedback from the experimenter takes the form of a simple positive or negative reward (correct or incorrect). The goal for the subject is to get as many "right" responses as possible. Initially, cards must be sorted according to, say, colour. When performance is successful, the "sorting rule" is changed, for example from colour to shape; the subject must notice the change and find the new rule. The global architecture of a network that passes the task comprises two distinct levels of organization: a low level (level 1) that governs the orientation of the organism toward an object with a defined feature and which would correspond to a visuo-motor loop, including visual areas and the premotor cortex; and a high level (level 2) that controls the behavioural task according to a memory rule, and which would be homologous to the prefrontal cortex or closely-related areas (Dehaene et al. 1987; Dehaene & Changeux 1989).

A key feature of the model is that the high level contains a particular category or cluster of neurons, referred to as "rule-coding clusters", each of which codes a single dimension (e.g., number, colour, or shape). During the acquisition step, the layer of rule-coding neurons is assumed to play the role of a "generator of diversity". The spontaneous activity then plays a critical role in the activation of a given rule-coding cluster; and because of lateral inhibition only one cluster is active at a time. A search by trial and error takes place, until a positive reward is received from the environment (here the experimenter). Then, the particular cluster active at this precise moment is selected (for discussion see Monchi et al. 2001; Asplund et al. 2010; Fuster 2008). The number of trials necessary to learn the current rule is small (1–2), and single trial learning may occur in normal subjects as it does with the model (Dehaene & Changeux 1991). This learning of short-term rules based upon the fast (millisecond to second) allosteric transitions of synaptic receptors may also be transferred to long-term stores as epigenetically-acquired patterns of connections (see above).

In the course of the modelling of the Wisconsin card-sorting task, an additional architecture was introduced in the form of an auto-evaluation loop, which can short-circuit the reward input from the exterior. It allows for an internal evaluation of covert motor intentions without actualizing them as behaviours, but instead by testing them by comparison with memorized former experiences (Dehaene & Changeux 1991).

In these early formulations, the "rule-coding clusters" were pre-wired in the neuronal network. Subsequent models, however, opened the range of possible epigenetic rules to a brain-wide space of combinations made available within the global neuronal workspace (Baars 1988). This is of importance when we consider the ability to coordinate thoughts or actions in relation to internal goals, which is referred to as "cognitive control" and is a rather infrequent phenomenon. This discussion thus illustrates how rules encoding ethical norms may originate from the brain. Against this background—which shows how ethical rules might be epigenetically built from brain organization—I propose the possibility of being epigenetically proactive, and adapting our social structures, in both the short- and long-term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of our brains.

4.2 A cascade model of top-down cognitive control

Cognitive control has been further investigated by Koechlin et al. (2003) using a set of more complex tasks than the Wisconsin Card Sorting Task, and which span (at least three) nested levels of complexity. They consist in the presentation of series' of coloured visual stimuli (squares or letters) organized into blocks, with an increasing importance of contextual signals: from "sensory control" with little if any contextual signal, to "contextual control" and, at the higher level, to "episodic control". Brain imaging fMRI recordings with healthy human subjects revealed that the lateral prefrontal cortex contributes to a hierarchical cascade of executive processes that involve at least three nested levels of processing. These are neurally implemented in distinct regions, from posterior premotor to rostral lateral prefrontal cortex regions (typically Brodman's area 46; Koechlin et al. 2003; Badre & D'Esposito 2007; Badre et al. 2009). Patients with focal lateral prefrontal cortex lesions performed cognitive tasks with sensory, contextual, and episodic deficits associated with focal damage to Brodman's areas 6, 45, and 46, respectively—as is expected from the cascade model (Azuar et al. 2014; Kayser & D'Esposito 2013).

By analogy with the Wisconsin Card Sorting Task (WCST) model mentioned above, behavioural rules are also sorted, but at different nested levels of information processing, the highest level rules "controlling" in a top-down manner the underlying rules closer to the senses. Hypothetically, ethical norms may be viewed as some particular kind of "control rules" developed within a social context, though this possibility still deserves to be explored by Koechlin, D'Esposito and colleagues.

Recently Collins & Koechlin (2012) have further suggested a computational model of human executive functioning associated with the prefrontal cortex, which integrates multiple processes during decision-making, such as expectedness of uncertainty, task switching, and reinforcement learning. The model reveals that the human frontal function may monitor up to three or four concurrent behavioural strategies and infers online their ability to predict action outcomes: whenever one appears more reliable than unreliable, this strategy is chosen to guide the selection and learning of actions that maximize rewards (see also Miller & Cohen 2001; Passingham 1993; Shallice 1988; Fuster 2008; Dehaene & Changeux 2011).

In their original paper, Collins and Koechlin do not explicitly mention social interaction. Yet we may consider an extension of their model to the social context by assuming that ethical or social norms are part of the "concurrent behavioural strategies" that they postulate exist in decision-making. The selection and learning of actions would then be more elaborate than the simple maximization of immediate rewards.

The developing baby is exposed very early on to a defined social and cultural environment, possibly even pre-natally (Lagercrantz & Changeux 2009; Lagercrantz et al. 2010). At this stage of development an intense synaptogenesis steadily occurs in the cerebral cortex, and epigenetic selection of neuronal networks accompanies the acquisition of the "maternal" language as well as of the common rules of the social community to which the child's family belongs. The developing baby/child is "impregnated" with the current ethical rules of the social community, and this is often linked with the symbolic (philosophical/religious) system of representation character of the community to which it belongs. These early traces may last for the lifetime of the individual and sooner or later create conflicting relationships with a fast-evolving environment aggravated by the increased longevity of the individual (Changeux 1985). On the basis of the neurobiological data mentioned above, one may define these rules as epigenetically-acquired patterns of connections (scaffoldings) stored in frontal cortex long-term memory, which frame the genesis of novel representation and "cognitively controlled" decision-making in a top-down manner.

Against this background I propose the possibility of being epigenetically proactive and adapting our social structures, in both the short- and the long-term, to benefit, influence, and constructively interact with the ever-developing neuronal architecture of our brains.

5 A naturalistic responsibility

5.1 Proactive epigenesis

The first sentence in the 1948 Universal Declaration of Human Rights states: "All human beings are born free and equal in dignity and rights."

Read as a description of the actual situation of human beings, this is blatantly and tragically false. Read as a normative ideal that we should strive for, it is noble but tragically unrealistic: considering our present cerebral structure, we are not likely to acknowledge in actual social practice the equal dignity and rights of all individuals independently of race, gender, creed, etc. Life conditions may have improved for many humans over time, yet the present global situation remains appalling, notably, with respect to poverty, unequal distribution of health care, and the predominantly non-egalitarian or bellicose relations between individuals or groups. The vast majority of human beings appear reluctant, unable to identify with, or show compassion towards those who are beyond (and sometimes even towards those who are within) *their* sphere. While some societies or individuals may be more prone than others to developing a strong ethnic identity, violence, racism, sexism, social hierarchies, or exclusion, all exhibit some form and measure of xenophobia.

What I have here suggested, however, is that we might make presently unrealistic ideals, such as equality in dignity and rights, somewhat more realistic by selecting them for epigenetic proactivity.

Synaptic epigenetic theories of cultural and social imprinting on our brain architecture open the door to being epigenetically proactive, which means that we may culturally influence our brain organisation with the aim of self-improvement, individually as well as socially, and change our biological predispositions through a better fit of our brain to cultures and social structures.

I suggest that certain areas of research are especially important to pursue with the goal of "epigenetic proaction" in mind. They aim at integrating recent advances in neuroscientific research into normative debates at the level of society. This does not necessarily mean that my level of explanation is "neurocentric" or "neuroreductionist". My aim is more "encyclopedic" in the sense that I wish to illustrate the benefits that neuroscience can bring to the humanities and social sciences and conversely. I do not see myself as either neuro-"centric" or "reductionist"—which would mean an exclusion of other categories of determinants at the social or historical levels—but I am more modestly willing to unify knowledge between the humanities and the neurosciences, which are too often deliberately omitted from the debate. This can be illustrated by two examples: violence in adolescents in relation to their social environments, and violence in adults associated with interconfessional conflicts.

Violence in adolescents is a common phenomenon in our societies and it is frequently repressed through police and judiciary means, often resulting in incarceration. But this approach to juvenile violence simply omits the scientifically-established fact that adolescence is also a time of "neurodevelopmental crisis". Evidence from anatomical and functional-imaging studies has highlighted major modifications of cortical circuits during adolescence. These include reductions of gyrification and grey matter, increases in the myelination of cortico-cortical connections, and changes in the architecture of large-scale cortical networks—including precentral, temporal, and frontal areas. (Klein et al. 2014). Uhlhaas et al. (2009) have used MEG synchrony as an indicator of conscious access and cognitive performance (rev. Dehaene & Changeux 2011). Until early adolescence, developmental improvements in cognitive performance are accompanied by increases in neural MEG synchrony. This developmental phase is followed by an unexpected decrease in neural synchrony that occurs during late adolescence and is associated with reduced performance. After this period of destabilization follows a reorganization of synchronization patterns that is accompanied by pronounced increases in gamma-band power and in theta and beta phase synchrony (Uhlhaas et al. 2009). These remarkable changes in neural connectivity and performance in the adolescent are only just being explored and may lead to special unexpected proactive care from society. In turn, this requires active research, including a social educative environment adequate to adolescents' special needs. This may include adequate physical exercise, cultural games, educational training, and new kinds of therapies yet to be invented.

Violent interconfessional conflicts have raged throughout human history. They continue to plague our modern societies and are presently an important cause of wars and other forms of violence throughout the world. One should remember that every newborn and child brain incorporates critical features of its biological, social, and cultural environment including, in addition to spoken and written language, symbolic systems and religious rituals (which include dietary and vestimentary practices as markers of the faith). These epigenetic traces are almost irreversibly laid down and may persist throughout the whole life of the individual. Yet they might be renewed through epigenetic transmission from adults to newborns. In this context, early proactive epigenetic imprinting through education is of critical importance. The aim of that education should not be to abolish faith or emotional convictions (e.g., moral, political, or religious) but only to control the fervour, intolerance, and fanaticism in their expression. The problem, as I see it, is not a belief itself, but the emotional intensity to which it gives rise and the manner in which it is expressed. Influencing a child brain to reduce its propensity to ideological violence or fanaticism and enhance its tolerance to others' differences also requires special proactive care from society that per force involves active research—including a social educative environment adequate to this particular goal.

These are only two illustrations of the many that are possible, chosen because they have been problematic throughout the history of humankind and show no signs of disappearing.

At the individual level, the social conditions of an infant, or an adolescent, are of crucial importance in their cerebral development, and adequate conditions can in principle be provided. The factual realism of this application is largely a matter of political will and social agreement. The scientific challenge will be to further develop the knowledge of these conditions and their effects on the developing infant and adolescent brain. Also, the challenge will be to develop our knowledge of how social conditions affect the adult brain, e.g., to prevent neurodegeneration.

On a more general level, when applied on a larger scale to a society, a population, or to the entire human species, the argument follows the same logic and is no less important—but it becomes considerably more complicated to apply, theoretically as well as practically.

If new cultural imprints were epigenetically stored in our brains (say, less violent or less sectarian features), future generations would presumably develop societies that reflect them (i.e., become more peaceful and inclusive). A weakness of this optimistic reasoning is its circularity, since we would already need to be peaceful in order for a peaceful society to be maintained. A crucial question then becomes: how long does it take for a cultural characteristic to leave a cerebral trace? In some measure stable and enduring cultural structures are needed in order to effect stable neurobiological changes and store cultural imprints in the brain that might give evolution a push in the right direction, but the chances of maintaining societies that conflict with the present nature of its inhabitants—say, maintaining a peaceful egalitarian rule in a society of violent xenophobes—are arguably slim.

The challenges involved in trying to be epigenetically proactive by culturally influencing the future actions of human genes and neuronal structures, with the aim of altering higher cognitive functions and their resulting behaviour seem formidable, at least if enlarged sympathy is on the agenda. Still, within the epigenetic neuroscientific framework, at least the theoretical possibility exists, and it is worthy of consideration by many other disciplines beyond neuroscience. Depending on how we choose to develop our culture, one day epigenetic rules that enlarge the presently-narrow realm of human sympathy might perhaps emerge.

5.2 Conclusion: A naturalistic responsibility

The origins of norms and the relationship between facts and values have been much debated in philosophy. Reasoning that weds scientific theory with normative considerations has been accused of committing the logical error of confusing facts and values, which is known as "the naturalistic fallacy".

The expression "the naturalistic fallacy" was coined by the British moral philosopher G. E. Moore and refers in his work to the identification (or reduction) of goodness with (or to) another property such as utility, pleasure, or happiness (Moore 1903). That issue is not relevant in the present context. In the interpretation of the naturalistic fallacy that is relevant here, the fallacy consists in deriving an "ought" from an "is", or a value from a fact, and letting descriptive properties entail normative properties, which confuses the distinction between facts and values in a fallacious manner. This argument is reminiscent of David Hume's claim that what *is* is entirely different from what *ought to be*, for "the distinction of vice and virtue is not founded on the relations of objects, nor is perceiv'd by reason" but is fundamentally a matter of feelings and as such is neither true nor false (Hume 1739, III, I). I agree that it is fallacious to derive "ought to be" from "is", and consider this a conceptual mistake that our theory of epigenetic proaction must and indeed does avoid. I do not assert that factual descriptions of the brain's architecture are tantamount to yielding recommendations or assertions of norms, do not confuse "is" with "ought", and consequently do not commit the naturalistic fallacy in this formulation.

We should observe that a *value* may be represented on many levels: non-conscious as well as conscious, as a basic biological function or as a feature of advanced moral reasoning. When discussing the naturalistic fallacy, value as a feature of advanced normative reasoning is the relevant sense of the term. The logical distinction between fact and value could collapse if the term is defined differently—say, if it features as a non-normative biological function. The logical error in the naturalistic fallacy concerns the fact/value distinction as it is drawn between normative and descriptive statements, namely between *ought* and *is*; not between facts that are/are not biological values, where that concern would presumably not arise.

However, eagerness to avoid the naturalistic fallacy must not prevent our normative reasoning from being informed by scientific theories. Normative judgments should be informed by facts, even though they cannot be entailed by them. If certain evaluative tendencies are innate in the normal human brain's architecture, such as self-interest and selective sympathy, this fact (if it is one) about the human being's neuronal structure would admittedly entail that every healthy, sufficiently mature individual will to some degree feel both self-interest and sympathy towards some other creature. However, this is not the entailment of a norm, but an empirical entailment of another fact. It does not entail that it is good (or bad), or that we ought to conceive it as good (or bad) that we are thus construed. Similarly, if it is true that we are, for example, and as we have argued, self-projective xenophobes, knowledge of this (presumed) fact is not in itself a justification of it. Understanding is not the same as justification: to know, or to understand, is not to approve. On the contrary, knowledge about our neural structures' predispositions should increase our awareness of the need for stable and realistic social structures and agreements to keep us in check.

We should also observe that a belief in the approximate universality of certain values, or preferential tendencies as innate features of the human neurobiological make-up, is logically compatible with a belief in maintaining the description/norm distinction.

My primary focus has been on the important empirical connections between biological facts and norms. Norms are brain constructs elaborated by human societies, biologically as well as culturally embedded in and constrained by the contingent evolution of socio-cultural structures—in particular, by the multiple symbolic philosophical and religious systems that have developed. This fact, and the realisation that normative judgments should be informed by facts even though they cannot be entailed by them suggests that science, philosophy and—not least—neuroethics—have a major responsibility: namely to decipher the network of causal connections between the neurobiological, socio-cultural, and contingent historical perspectives that allow a moral norm to be enunciated at a given moment in human history; and to evaluate their "universal" character as pre-specified in our genome and shared by the human species in distinction from those relative to a given culture or symbolic system. The "fallacy" of the naturalistic approach is thus inverted into a naturalistic responsibility (Evers 2009): the responsibility to connect facts and values, biology, and socio-cultural structures, and to use that enriched understanding for the benefit of ourselves and our societies.

We may hope that through the rational exchange of arguments between partners with different cultures and moral traditions debating together, a species-specific "human core" could become dominant beyond individual differences and converge on a common structure (Changeux & Ricoeur 2000). At the same time, we must note that the diversity of human individuals and societies is enormous and must be respected while we strive to find this common ground that might allow coexistence.

The idea of proactively selecting those specific dispositions or capacities (such as sympathy) that we all share as human beings which that, if properly developed, may benefit our global co-existence while respecting individual and ideological diversities, is well in line with Darwin. Darwin wrote in The Descent of Man:

> As man advances in civilization, and small tribes are united into larger communities, the simplest reason would tell each individual that he ought to extend his social instincts and sympathies to all members of the same nation, though personally unknown to him. This point being once reached, there is only an artificial barrier to prevent his sympathies extending to the men of all nations and races.

Lewontin (1993) argues that while traditional Darwinism has portrayed the organism as a passive recipient of environmental influences, a correct understanding should emphasize that humans are active constructors of their own environment—in particular the social and cultural environment. I agree and argue further that, in line with Darwin, we can be active constructors of our own brains through using our environment and culture, in a relationship that is reciprocal.

In this article, my main focus has been on feasibility—that is, on whether we *can* be epigenetically proactive. If we assume an affirmative answer to that question, an important follow-up question arises: whether we *should* be so. My basic position, that I have here tried to express, is that epigenetic proaction could be a very promising, powerful, and long-term way of influencing human nature and of improving our societies. However, in order to pursue this in a responsible and adequate manner, caution is required, along with careful analyses of the relevant social and ethical issues. Science can be, and has throughout history repeatedly been, ideologically hijacked, and the resulting dangers increase with the strength of the science in question. If, say, humans learn to design their own brain more potently than we already do by selecting what we believe to be brain-nourishing food and pursuing neuronally-healthy life-styles, we *could* use that knowledge well—that is, there is certainly room for improvement. On the other hand, the dream of the perfect human being has a sordid past, providing ample cause for concern about such projects. Historic awareness is of the utmost importance for neuroethics when assessing suggested applications in a responsible and adequate manner. Moreover, what we mean by “responsible and adequate” is open to interpretation. The traits we choose to favour epigenetically, and the social structures we choose to develop, depend on who “we” are, and in what society we wish to live.

Arthur Koestler compares evolution to “a labyrinth of blind alleys” and suggests that “there is nothing very strange or improbable in the assumption that man’s native equipment, though superior to that of any other living species, nevertheless contains some built-in error or deficiency which predisposes him to self-destruction” (Koestler 1967, xi). In that light, steering evolution by influencing the cultural imprints to be stored in our brains appears to be an attractive option.

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