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Opinion

Climbing Brain Levels of Organisation from Genes to Consciousness

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Given the tremendous complexity of brain organisation, here I propose a strategy that dynamically links stages of brain organisation from genes to consciousness, at four privileged structural levels: genes; transcription factors (TFs)–gene networks; synaptic epigenesis; and long-range connectivity. These structures are viewed as nested and reciprocally inter-regulated, with a hierarchical organisation that proceeds on different timescales during the course of evolution and development. Interlevel bridging mechanisms include intrinsic variation-selection mechanisms, which offer a community of bottom-up and top-down models linking genes to consciousness in a stepwise manner.

Understanding the Human Brain

Several international research programs aim to advance understanding of the human brain and its functions by using multidisciplinary approaches, including information technologies. Yet, contemporary brain sciences face serious difficulties. For instance, at the experimental level, most *in vivo* data originate from behavioural, electrophysiological, or brain imaging recordings, with little reference to the molecular level that is so essential for drug design. From a theoretical and modelling perspective, additional difficulties are encountered. For instance, microprocessors are claimed to fall short in representing synaptic and neuronal dynamics [1]; in addition, the use of **Bayesian statistics** (see Glossary) is criticised in the modelling of cognitive processes [2]. Moreover, modelling studies often disregard the evolutionary and developmental dynamics of brain hierarchical organisation and their underlying molecular mechanism. Thus, there is an urgent need to integrate concepts and data from the disparate and highly individualised brain science disciplines within a unified framework of brain biology. Here, I delineate some of these difficulties and suggest plausible strategies to bridge the divide between the fast-moving extremes of the field: genes at one end, consciousness at the other. The challenge is to link the multiple 'brain pictures' arising from current approaches, not necessarily into a unique model, but into a coherent and open community of brain models.

Nesting Models of the Brain

Brain network models typically comprise assemblies of interconnected neurons with algorithmically defined function amenable to formal computation [3]. This mode of description faces the complexity of an arrangement of 100 billion neurons that arose over a million years of evolution and almost 15 years of individual postnatal development. A possible strategy is to penetrate the jungle of brain physical organisation and tangentially cleave it into multiple nested levels of structural organisation [4]. The definition of a given level classically relies upon the structural (anatomical) characteristics of its elementary components and the particular functions (or properties) unique to that level, each higher level proceeding from elements of a lower level and serving further integrated functions above. Moreover, the models aimed at representing and/or simulating a process and/or behaviour on the basis of minimal, yet realistic,

Trends

The proposed approach is to nest the various intertwined structural and functional levels that compose the brain into a coherent and open 'brain models community' covering multiple timescales.

A critical bridging role between the gene and neuronal levels is assigned to regulatory proteins termed 'TFs'.

TFs regulate disparate genes into coherent assemblies.

The impact of the environment on brain synaptogenesis is modelled as activity-dependent selective stabilisation pruning of synapses.

Long-range connectivity, subject to developmental shaping through interactions with the physical, social, and cultural environment, is proposed to form the bridge between neuronal microcircuitry and higher cognitive functions by globally integrating the underlying neural organisations.

A novel allosteric pharmacology of TFs is proposed for neuropsychiatric diseases.

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 http://dx.doi.org/10.1016/j.tics.2017.01.004

architectures and activity patterns most often use a single level of organisation. To attempt a type of modelling that spans several levels, as proposed here, is in itself a theoretical position.

The approach presented here, which may be called a 'dynamical nesting of models', assumes that the brain is a nested assembly of functional structures at multiple levels of organisation, from molecules to consciousness, reciprocally inter-regulated and in constant dynamic evolution, which operates intrinsically through variation-selection mechanisms yet on different timescales, from the million years of human ancestry up to the 100 ms of psychological operations. This generalised '**Darwinian' paradigm** [5–11] implies that, at successive levels of organisation, the processes of variability, selection, and amplification occur and establish close inter-relationships between developing and adult brains and the constantly evolving physical, social, and cultural environment. Such interactive processes are expected to leave anatomical and functional traces within the eminently variable architecture of each individual brain. Given that the spectrum of organisation levels is broad, only four have been selected and are discussed at the risk of being incomplete and biased (Figure 1).

In the brain, the macromolecular level has a fundamental role by imposing inescapable physical constraints upon even the highest levels: for instance, the evolution of the species-specific features of the brain is grounded in genes. The dynamics of signal transduction by receptors and ion channels limit the dynamics of information processing by the brain to the speed of sound, while our computers operate at the speed of light. All brain functions, including the highest, are necessarily rooted in the physics and chemistry of their basic macromolecular components. Furthermore, the system of **TFs**, which underpins cooperative networks of gene

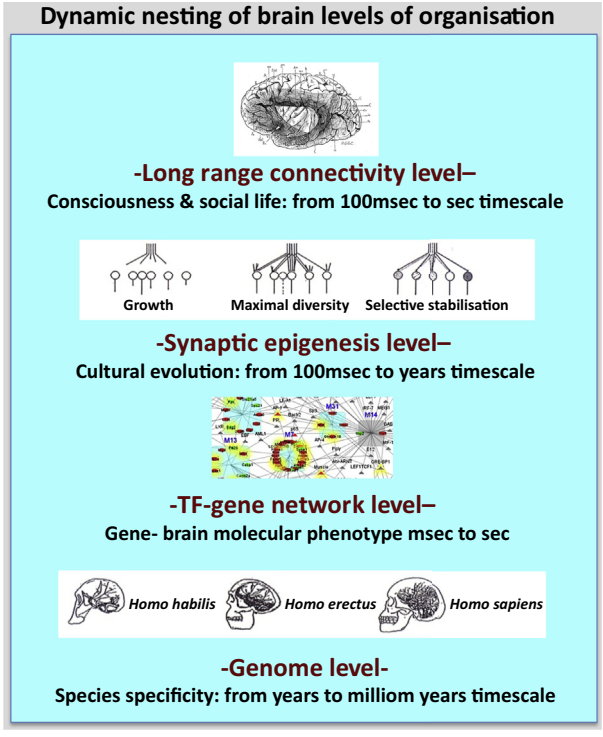

Figure 1. Dynamic Nesting of Brain Levels of Organisation. A schematic view of the proposed model of nesting levels of brain organisation and their inter-relationships. As indicated, only a few levels have been selected, on both sides of the neuronal level, but with distinct building blocks and timescale dynamics. For further explanation, see the main text.

Glossary

Alexia: in pure alexia, individuals have severe reading problems due to cerebral lesions, while other language-related skills, such as naming or writing, remain intact.
Allosteric interaction: in contrast to the competitive steric interaction between ligands for a single site, an allosteric interaction occurs between topographically distinct binding sites and is mediated by a conformational change.
Bayesian statistics: a theory in the field of statistics in which the evidence about the true state of the world is expressed in terms of degrees of belief, known as Bayesian probabilities. Bayesian inference is specifically based on the use of Bayesian probabilities to summarise evidence. It is no more than a method of calculus.
Darwinian mechanism: an evolutionary mechanism inspired by the theories of Charles Darwin on the evolution of species but not necessarily occurring at the gene level: for example synapse selection (or neural Darwinism) in the nervous system.
Diffusion tensor imaging tractography (DTI): a magnetic resonance-based neuroimaging technique based upon the observation that parallel bundles of axons and their myelin shield facilitate the diffusion of water molecules along their length, making it possible to visualise white matter tracts in the brain.
Degeneracy: a code that is degenerate is one in which several code words have the same meaning. The genetic code is degenerate because there are many instances in which different codons specify the same amino acid. According to the neural Darwinism model, the neural code is degenerate in the sense that different neuronal networks might code the same meaning.
Evolutionary parsimony: the absolute number of structural coding genes in the genome of vertebrates is relatively small (20 000–25 000) and has not significantly changed during the course of mammalian evolution despite a dramatic increase in brain complexity.
Global neuronal workspace (GNW): the global neuronal workspace, in which conscious processes are assumed to occur,