Editorial

An Enduring Challenge: The Structure-Function Relation in the Brain and the 'Very Large Brain Projects'

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THE VERY LARGE BRAIN PROGRAMS

How the structure of the brain relates to its function has been and still is the major challenge in neuroscience. This question was at the root of neuroscience and has been the golden thread in the history of brain studies ever since (*e.g*. see for example the excellent monograph of Charles G. Gross on 'tales in the history of neuroscience' [1]). Several obstacles make this problem particularly challenging and despite an enormous progress in modern brain research, we still struggle to improve our understanding. To make progress along this line,'very large brain programs' (VLBP) have been launched within this decade. Among others, the US based Human Connectome Program (HCP) [2] and the European Human Brain Project (HBP) [3] set the first large initiatives (see [4] for a recent summary of emphases and funding characteristics of nine major world-wide brain projects).

Now, some years after the initiation of these programs several critical aspects have emerged that are, in some ways, a reflection of a deeper grounded and ever competing dichotomy in brain science: simply, technical reconstructions based on the 'brain as a computer metaphor', versus attempts to understand how the brain connects the informational structure with its phenomenal constructs, such as perception, cognition, consciousness, agency and free will: An engineering demonstration on one hand opposes a deeper grounded scientific and philosophical endeavor. The money is, what else can we expect, mostly on the engineering side. From this side the Swiss founded 'Blue Brain Project' around Henry Markram, who also raised the Human Brain Project, has very recently published the first remarkable results on a computer reconstruction and simulation of a connectome containing 30.000 rat brain neurons in the journal *Cell* [5]. Again, despite the enormous effort and technical achievements behind this work, doubts have been raised whether the results can shed more light on the function that this piece of sensory cortex may represent [6, 7].

There is obviously more behind the question of structure-function relations in the brain than meets the eye of a pure technical reconstruction. Models of the human and rodent connectome (*i.e*. the brains wiring pattern) may slowly emerge from the work behind very large brain projects. But, does our understanding of brain function progress in the same way? Is the cell-signaling structure, the wiring pattern of the brain, a complete embodiment of its function? Not to get it wrong: I do not want to critically overlay the concerted efforts of the VLPS, nor do I undermine the possible progress that must be expected in the face of the investments made. The point that I do want to raise here is, that there is something missing within attempts that solely build on the 'informational structure', the *contents of information* behind the wiring pattern of the brain. What is missing is the '*meaning'* behind this information. The brain combines information-based properties with experiential phenomenology. Quite opposing characteristics are cross-linked by the structure-function relation of this remarkable organ. How the brain can actually combine two opposing characteristics, crossing the Rubicon separating two mutually incompatible magnitudes, may represent an indispensable working principle that should be at the center of attention in brain studies. Because largely neglected, this point deserves a few more considerations.

RESOLVING DUALITIES

Dualities pervade brain science at different levels of organization and from different methodological perspectives. This is also reflected within the history of

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Neuroscience during the nineteenth and twentieth century. Cortical localizations were followed by the holistic tradition of anti-localizationists and vice-versa [1]. The integration of both aspects eventually led to the prevalent view today, that cortical segregation and functional dispersion provide the substrate that continually interacts and becomes integrated into the construct that accompanies a conscious perceptive state (cPS). Today, with the help of non-invasive neural activity measures, such as fMRI or EEG, we know that dissociations in perception, from unconscious and subliminal to fully conscious states, map well onto the spatio-temporal variation of the underlying neuronal firing pattern [8, 9]. Again, the duality of these findings rests in the difference between the statistical nature behind information based observations on one hand and the 'expectation' provided by the organization of a perceptive brain, as reflected by Friston's 'free-energy principle' model [10].

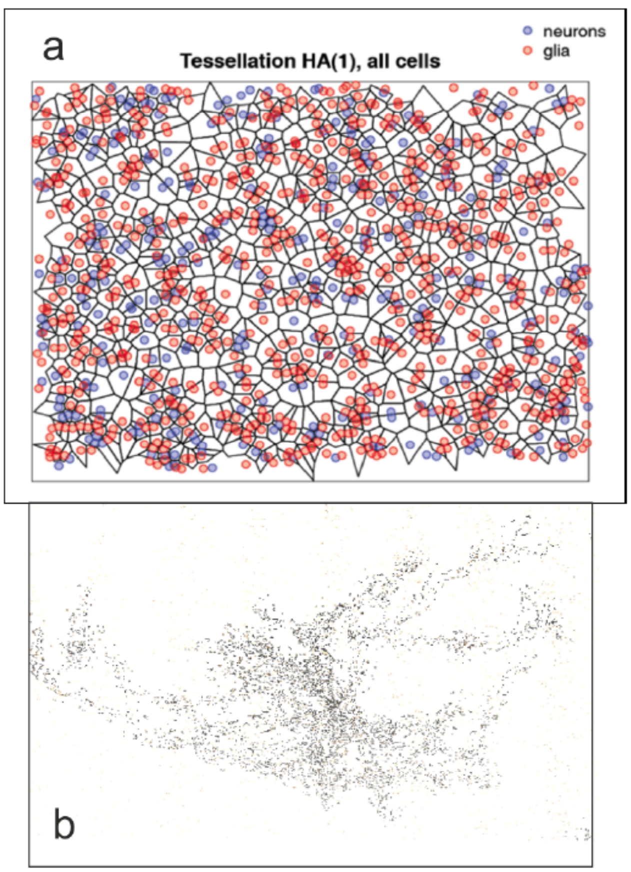

Figure: (**a**) Voronoi- Tessellation of the somatic (cell-body) domain of neurons (blue) and glia (red) cells in the non-laminated, nucleated avian hyper-pallium, a homolog structure of the mammalian neocortex. Below (**b**) an impression of a possible synaptic domain of just a single neuron in matching extension is demonstrated. Note: the 'functional volume' of just a single cell (including all input and output peripheries) extends over domains of entire cell populations.

ONE TO MANY: STRUCTURE AND FUNCTION

The most radical version of opposing properties lies in the core of the 'degenerate nature' [11], of the 'one to many relation' between structure and function in the brain, as again Karl Friston has suggested [12]. A huge functional repertoire resides in the brains fixed architecture. To eventually elucidate the relationship between the structural connectivity of the brain ('the one') with the richness behind its function ('the many'), we eventually have to resolve several questions that are unique to the properties of the brain. For example, the structure-function divide is characterized by an enormous complexity behind the organization of cells and their pre-and postsynaptic periphery. The 'functional volume' of just a single cell, involving all its peripheral in-and output relations, can in fact extend over the entire geometry of its reference structure *e.g*. over the entire brain (see the Figure above with left) [13]. This situation is unique to the brain. However, in order to explain the one-to-many relation of structure and function, we have to go one step further. In my view, this particular relation cannot become clarified by studies restricted to the reconstruction of the 'information processing domain' at a single scale (the cell-scale, the macro- and microcircuits of connections). Instead, such an attempt will have to involve many action orders of physical scales, ranging from the entire brain down to the molecular and sub-molecular (atomic-) level. Also a special type of dynamics behind the multiple scaled neuronal organization starts to play a central role. In an upcoming article in Biophysics of Consciousness [14] I suggest that a dissipative dynamic self-assembly at the atomic scale that is associated with ion conduction of neuronal signaling membranes, may be a candidate process that can combine the opposing characteristic of brain structure and function. We surely have to go beyond the type of network reconstructions, which are at the center of the very large brain projects to eventually deepen our insight into the way the brain models the world.

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