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František Baluška & Stefano Mancuso

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Opinion Article

Deep evolutionary origins of neurobiology

Turning the essence of 'neural' upside-down

František Baluška^{1,*} and Stefano Mancuso²

¹University of Bonn, IZMB; Bonn Germany; ²University of Florence, LINV; Florence Italy

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It is generally assumed, both in common-sense argumentations and scientific concepts, that brains and neurons represent late evolutionary achievements which are present only in more advanced animals. Here we overview recently published data clearly revealing that our understanding of bacteria, unicellular eukaryotic organisms, plants, brains and neurons, rooted in the Aristotelian philosophy is flawed. Neural aspects of biological systems are obvious already in bacteria and unicellular biological units such as sexual gametes and diverse unicellular eukaryotic organisms. Altogether, processes and activities thought to represent evolutionary 'recent' specializations of the nervous system emerge rather to represent ancient and fundamental cell survival processes.

Lessons from Bacteria

From communicative behavior, via 'social cognition to intelligence'. Despite their organismal simplicity, bacteria perform complex communications allowing them to deal with complex environment. Bacteria use special chemical 'language' known as quorum sensing to exchange relevant information and coordinate bacterial populations into supracellular assemblies¹⁻⁵ resembling multicellular organisms.⁶ Bacteria communicate also with eukaryotic hosts.⁷⁻¹² Signal transduction in bacteria resembles neural networks.¹³⁻¹⁹ Bacteria sense effectively diverse parameters from their environment and their cognitive²⁰ and intelligent^{13,15} behavior implicate that life has neural features already at the prokaryotic level. For example, information processing by cyanobacteria during their adaptation to phosphate fluctuations involves distinct adaptive modes acting as 'experienced' self-constitution of organism under fluctuating environment.²¹ It is relevant in this respect that several proteins mediating neurotransmission across synapses in brains have been found in bacteria too.^{22,23}

Studies on bacterial resistance to diverse antibiotics concluded that bacteria actively resist these antibiotics via 'cognitive' and 'intelligent' activities including innovation, anticipation and learning.^{24,25}

Lessons from Unicellular Eukaryotes and Gametes

Swimming and crawling of unicellular 'neurons' showing 'cognition and intelligence'. Neural parallels are even more convincing in unicellular eukaryotic organisms. For example, ciliate protozoan *Paramecium* has been devoted a whole chapter in the recently published book, *An Introduction to Nervous Systems*.²⁶ Although not covered in detail here, there are several other convincing examples of swimming unicellular eukaryotes with similarly complex sensory and neuronal behavior such as, for example, predatory *Euglena* or green alga *Chlamydomonas*. These have even so-called 'eye-apparatus', which commands, via photo-induced intracellular electric signals, their motor motoric flagella.^{27,28}

Another example of unicellular eukaryotic organisms clearly showing neural behavior is amoeba *Physarum polycephalum*. This smart organism even solves geometric puzzles if allowed to show his abilities using clever experimental systems.²⁹⁻³³ This 'cognitive' smartness and behavioral 'intelligence' of this rather unspectacular organism resembling large aggregate of protoplasm is truly amazing. Crawling over agar plates, it shows unicellular forms of 'learning', 'memory', 'anticipation', 'risk management', and other aspects of 'intelligent behavior'.²⁹⁻³⁵

Finally, gametes of multicellular organisms express diverse neuronal molecules which underlie cell-cell communication, chemotaxis and other aspects of sexual reproduction in animals.³⁶⁻⁵² For instance sperm cells and oocytes express numerous neurotransmitters and their receptors.³⁶⁻⁴⁸ These are involved, for example, in sperm acrosome reaction after sperm cells successfully identify and approach the receptive oocytes.^{37,44,49-52}

Lessons from Plants

Root apex cells versus neurons. Recent advances in plant cell biology and neurosciences reveal surprising similarities between plants cells and neurons. They are inherently polar, with signal input and signal output poles, secrete signaling molecules via robust endocytosis-driven vesicle recycling apparatus, and are capable of sensory perception and integration of these multiple sensory perceptions into adaptive actions which serve for survival of organisms harboring these cells specialized for signaling and communication.⁵³⁻⁶² Moreover, neurons and plant cells have in common abilities to generate spontaneously action potentials which convey electric signaling across tissues of multicellular organisms (for plant cells, see refs. 63 and 64).

*Correspondence to: František Baluška; University of Bonn, IZMB; Kirschallee 1; Bonn, D-53115 Germany; Tel.: +49.228.734761; Fax: +49.229.739004; Email: Baluska@uni-bonn.de

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Of course, plant cells do not extend long projections as neural axons or any similar protrusions—they do not need this as the polarized plant cells are arranged within regular cell files where pre-synaptic poles closely adhere to post-synaptic poles.^{53,54,65,66}

In plants, neuronal features are especially prominent in root cells of the transition zone interpolated between the apical meristem and elongation region.⁶⁷⁻⁷⁰ Multifunctional signaling molecule auxin emerges as plant-specific neurotransmitter which is secreted by pre-synaptic poles of the transition zone root cells and is eliciting electric responses and calcium, ROS and NO based signaling cascades at the post-synaptic domain of adjacent cells.^{53,65,68,69,71-74}

Plant neurobiology, kin-recognition, cognition and plant intelligence. Keeping in mind the surprising neuronal achievements of bacteria and unicellular eukaryotes, it should not be a big surprise to learn that also plants show most of these features. In fact, there are several recently published, but also older, data demasking plants as sensitive organisms enjoying almost all relevant neuronal features,^{63-68,75,76} including ‘kin-recognition’^{77,78} and plant-specific form of ‘intelligence’.⁵⁹⁻⁶¹ Nevertheless, plant neurobiology experiences difficult start^{62,79,80} which is related to deeply-rooted, almost ‘dogmatic’, view of plants as passive creatures not in a need of any neuronal processes and capabilities.⁷⁹ One can trace this strong belief back to Aristoteles,^{81,82} who makes clear that it will be rather tough to break this spell despite the fact that one of the first attempts to rehabilitate plants was done by nobody less than Charles Darwin.⁸³ Charles Darwin proposed that the root apex represents the brain-like anterior pole of the plant body^{83,84} and our recent data support this proposal strongly.^{53,65,68,69,85,86}

Lessons from Sessile Animals

‘Young brain’ and ‘brain with anus’ concepts. Recent surprise comes from analysis of gene expression patterns relevant for brain, heart, and the anterior-posterior axis. The Hydra ‘foot’ emerges as the most anterior part of the Hydra body whereas original ‘mouth’ turns into the posterior pole, and corresponds to ‘anus’.⁸⁷⁻⁸⁹ Consequently, the brain emerges as the oldest part of metazoan body.⁸⁷ Importantly, not just Hydra but all sessile animals are anchored in substrate via the anterior poles of their bodies⁹⁰ (for overview see Dawkins⁹¹). Interestingly in this respect, these sessile marine animals reproduce via small swimming larvae, which settle down to substrates with their anterior poles. Moreover, neurotransmitters like serotonin^{92,93} and neuropeptides⁹⁴ are relevant for neurons-driven settlement of sensory-primed larvae and subsequent metamorphosis. Similarly in sessile marine algae like *Ulva*, swimming zoospores settle via sensory cues with their anterior pole to the substrate.⁹⁵ This fits nicely with the plant body having the root pole as anterior-neural part and the shoot pole as posterior-sexual part⁵⁴ (see also refs. 83–85). Interestingly in this respect, monospores of marine red alga *Porphyre yezoensis* assemble dense F-actin meshworks at their anterior poles.^{96,97} During settling, the adhesive pole becomes the F-actin-enriched pole, suggesting that the F-actin rich anterior pole is corresponding to the substrate-settled pole.⁹⁷ All these examples implicate that in most settled multicellular organisms, irrespective if plants or animals, the anterior pole is penetrating substrate anchoring the whole body in fixed position. Settled and anchored anterior pole then accomplishes filter feeding in plants as well as in some sessile animals.^{90,91}

Table 1 **Plant-like features in sessile animals**

1.	Sessile Lifestyle
2.	Phenotypic Plasticity
3.	Modularity and Metamers
4.	Cell-Cell Channels
5.	Vascular Systems Driving Solutes
6.	Secondary Metabolites
7.	Continuous Exo-Skeletons
8.	Feeding via Filtrating Solutes
9.	Photosynthetic Symbionts
10.	Asexual Clonal Reproduction
11.	Totipotency
12.	High Longevity
13.	Only Innate Immunity
14.	Predator-Induced Defence
15.	High Capacity for Regeneration
16.	Apical Growth Zones
17.	Opening Pores at Surface
18.	No Sensory Organs
19.	Allegedly no Neural Systems

All these features are pooled from several different sessile animals.

Corals and Trichoplax

Complex neurobiology gene networks ‘without’ neurons and brains. Recent genomic analysis and projects resulted in surprising neuronal complexity which was not expected in these sessile (corals) or only slowly moving (Trichoplax) multicellular animals.⁹⁸⁻¹⁰³ As they are believed to lack brains (corals) and even neurons (Trichoplax) and, similarly as plants, considered not to be in any need of neurobiological apparatus due to sessile life-style; these data represent new challenge for the neurosciences. Until now, neurosciences typically associate complex neural systems with movements of evolutionary more advanced organisms; with humans at the top, being considered for the only organism having higher levels of consciousness.^{82,104}

Importantly, as sessile multicellular animals show almost all ‘so-called’ plant-specific features (Table 1), the profound differences between animals and plants are, in fact, rather secondary features of their sessile life-style. They do not represent, as generally accepted, the plant-animal schism, which can be traced back to Aristoteles and his philosophy.^{81,82}

Evolution of Action Potentials from Evolutionarily Ancient Plasma Membrane Repair Processes?

In an attempt to explain existence of action potentials in walled plant cells, Andrew Goldsworthy proposed in his very stimulating theoretical article that plant action potentials evolved from ancient repair mechanisms coping with numerous injuries early cells were facing.^{105,106} He proposed in this concept that membrane depolarization, which is accompanying these rapid electrical signals, is needed for repair of damaged membrane. Although the primary function of action potentials was to depolarize membrane to allow its repair, such electrical signals running from sites of injury turned-out

to be very useful communication pathway for intracellular as well as transcellular signaling. In support of this attractive concept, intracellular action potentials are linking the eye apparatus of unicellular algae with the flagellum in sensory-motoric circuit.^{27,28} Moreover, putative intra-neuronal action potentials underlie intracellular electrical communication between synapses and nuclei.¹⁰⁷ Importantly, cell membrane resealing was reported to be accomplished via vesicular recycling mechanism closely resembling neuronal synaptic activity.¹⁰⁸ In addition, plant synaptotagmins are also relevant for vesicular repair processes at the plasma membrane suffering from stress-induced damages.¹⁰⁹ Obviously, processes thought to represent evolutionary 'recent' specializations of the nervous system emerge, in fact, as ancient and fundamental cell survival processes.

Interestingly, anesthetics are diverse substances which can quickly and reversibly switch off consciousness in humans, as well as to compromise evoked and spontaneous motor responses in animals, tactile plants, ciliated protists.¹¹⁰⁻¹¹⁷ Recently, it has been proposed that the capacity to respond to anesthetics arose already in unicellular organisms¹¹⁰ as an adaptation to boundary membrane homeostasis and ion channels activities to changing environmental conditions.¹¹⁰⁻¹¹² Importantly, this concept implicate existence of endogenous anesthetics-like substances. Plants are very informative in this respect. Endogenous levels of ethylene, which is considered by plant sciences only as plant stress hormone, increase rapidly in plant cells and tissues suffering from diverse stress situations.¹¹³ Intriguingly in this respect, ethylene belongs also to very effective anesthetics and was even used in medicine several decades ago.^{114,115}

Non-Genomic Sensory Perceptions Are an Integral Part of Neural Information

When sensory events change structures, neurons, brains and organisms. Biological systems actively experience environment, both abiotic and biotic, and store (memorize) the obtained information in form of embodied knowledge.¹¹⁸⁻¹²⁰ Via active accumulation of sensory-mediated experiences, sensory cells (neurons) change their structure, development, cell-cell communication (synaptic plasticity), as well as their activities and future fates.¹²¹⁻¹²⁴ This important phenomenon is obvious already at subcellular levels such as cilium of sensory neuron which are not static structures but plastic antennae whose structure and function depends on the history of perceptions and signaling activities.^{125,126} As sensory perceptions and experiences represent non-genomic information;¹²²⁻¹²⁷ neurons, brains, plants and their cells, as well as bacteria and their colonies are phenotypically plastic.^{121-124,128,129} They are less hard-wired genetically but shaped structurally via experience-dependent *neural processes* based on sensory perceptions received from environment.¹²²⁻¹²⁴ As it is the case of developmentally open and plastic plants;^{84,86,129,130} also neurons, their networks, and animal brains are shaped besides genetically (*Aristotelian* bottom-top direction) also environmentally (*Platonian* top-down direction).¹²¹⁻¹²⁴ This feature makes the essence of sensory networks for unique realm in biology, realm which is not reserved only for humans or animals, realm which spans across all biological levels, and realm which is evolutionarily as ancient as the life itself. Obviously, as stated also by Szentágothai and Érdi,¹³¹ the essence of neural needs revision and re-examination in biology.

Current Biology Needs to Complete the Paradigm Shift Initiated by Galileo Galilei and Charles Darwin

As mentioned above, contemporary biology is still trapped in Aristotelian paradigm that plants differ profoundly from animals due to their insensitive nature and lacking the abilities to actively reconstruct environment from past sensory experiences in order to perform adaptive behavior allowing survival despite challenging environmental conditions. Recent advances in plant sciences have revealed that the sensory plants do not differ profoundly from the sensory animals.^{53-62,68,69,74-78} Close similarities in sensory and neurobiological aspects are at odd with the currently dominating evolutionary ideas about plants and animals (example in Baldauf and Palmer¹³²). However, plants and animal share several complex and conserved features, missing from fungi and unicellular organisms, suggesting that they might be phylogenetically much more closely related.^{133,134} Alternatively, these neuronal similarities between plants and animals are results of convergent evolution. Irrespective if these similarities are result of homologous or analogous structures and processes, examples of bacteria and unicellular eukaryotic organisms enjoy cognitive and sensory complexities, underlain by numerous neuronal proteins and sensors, implicate that we need to reconsider the evolutionary origin of neurosciences.

As the Aristotelian heritage is robust, due to long history of sciences,^{82,135} it is obvious that this paradigm shift in biology will be as complicated as that accomplished in physics when the Aristotelian geocentrism world-view was abandoned in favor of the heliocentrism. But this time also the human nature is directly involved and questioned. Science is inevitably subjective human activity, which has produced our current anthropocentric world-views. As a consequence, this biological paradigm-shift necessary to escape from the Aristotelian trap might turn out to be even more complicated and difficult one as the physical paradigm shift. In fact, it started with Charles Darwin some 150 years ago and is still not completed.

As Michael Pollan stated, the 'disease of human self-importance' is firmly rooted in our scientific thinking. We still did not 'digested' lessons from the Darwinian revolution 150 years ago that humans are only 'one fiber in the fabric of life' in which evolution and co-evolution is working on us in the same way as it is working on all others.¹³⁶ Looking at the outside world from the 'plant perspective'¹⁰⁷ reveals that plant-human interactions are much more complex providing effective 'cure' for the disease of 'human self-importance'.¹³⁷ Plants provide reward to their pollinators in form of attractive flowers and tasteful foods. Crop plants such as wheat, maize, and rice belong to evolutionarily most successful species on the Earth. Co-evolution of humans with plants, as well as existence of numerous psychoactive mind-altering plant substances suggest that plants contributed significantly to our evolution and that plants may actively interfere into our sensory faculties. In fact numerous plant substances are powerful enough to change our sensory experiences and to modulate our world-view. Recent discovery of cannabis from 2700-year-old Yanghai Tombs in China reveal that ancient human civilizations employed psychoactive plants¹³⁸ which can be expected to have shaped their cultures significantly.¹³⁹ In future, we should be open minded to investigate these aspects as they might tell us more not only about plants but also much more about the human nature too.

It was Galileo Galilei who first made clear statements that our human senses allow us only subjective perceptions.^{140,141} With this view, which contrasted strongly with the classical Aristotle-based tradition that human senses are objective attributes, Galileo can be considered as father of the modern neurosciences.^{140,141} Therefore, we should be aware that any living unit equipped with complex sensory systems and organs is ‘constructing’ its own world-view which might be radically different, but principally not better or worse, from our human-specific world views.

Note

A glossary of terms can be found at:

www.landesbioscience.com/supplement/BaluskaCIB2-1-sup.pdf

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