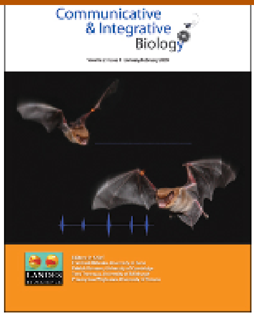

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Communicative & Integrative Biology

ISSN: (Print) 1942-0889 (Online) Journal homepage: http://www.tandfonline.com/loi/kcib20

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To cite this article: František Baluška & Stefano Mancuso (2009) Deep evolutionary origins of neurobiology: Turning the essence of 'neural' upside-down, Communicative & Integrative Biology, 2:1, 60-65, DOI: 10.4161/cib.2.1.7620

To link to this article: https://doi.org/10.4161/cib.2.1.7620

[Communicative & Integrative Biology 2:1, 60-65; January/February 2009]; ©2009 Landes Bioscience

Opinion Article

Deep evolutionary origins of neurobiology

Turning the essence of 'neural' upside-down

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Key words: bacteria, evolution, neuron, neurosciences, plants

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 assemblies[1-5] 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 cognitive[20] 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]

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Submitted: 10/8/08; Revised: 12/15/08; Accepted: 12/15/08

Previously published online as a *Communicative & Integrative Biology* E-publication: http://www.landesbioscience.com/journals/cib/article/7620

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).

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 bodies[90] (for overview see Dawkins[91]). 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 neuropeptides[94] 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 part[54] (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 organisms[110] 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 Palmer[132]). 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 plants[138] 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

References

1. Crespi BJ. The evolution of social behavior in microorganisms.Trends Ecol Evol 2001; 16:178-83.
2. Ben Jacob E, Becker I, Shapira Y, Levine H. Bacterial linguistic communication and social intelligence. Trends Microbiol 2004; 12:366-72.
3. Visick KL, Fuqua C. Decoding microbial chatter: cell-cell communication in bacteria. J Bacteriol 2005; 187:5507-19.
4. Waters CM, Bassler BL. Quorum sensing: cell-to-cell communication in bacteria. Annu Rev Cell Dev Biol 2005; 21:319-46.
5. Shapiro JA. Bacteria are small but not stupid: cognition, natural genetic engineering and socio-bacteriology. Stud Hist Philos Biol Biomed Sci 2007; 38:807-19.
6. Shapiro JA. Thinking about bacterial populations as multicellular organisms. Annu Rev Microbiol 1998; 52:81-104.
7. Joint I, Tait K, Callow ME, Callow JA, Milton D, Williams P, Cámara M. Cell-to-cell communication across the prokaryote-eukaryote boundary. Science 2002; 298:1207.
8. Joint I, Tait K, Wheeler G. Cross-kingdom signaling: exploitation of bacterial quorum sensing molecules by the green seaweed Ulva. Philos Trans R Soc Lond B Biol Sci 2007; 362:1223-33.
9. Leveau JH, Lindow SE. Utilization of the plant hormone indole-3-acetic acid for growth by Pseudomonas putida strain 1290. Appl Environ Microbiol 2005 71:2365-71.
10. Federle MJ, Bassler BL. Interspecies communication in bacteria. J Clin Invest 2003; 112:1291-9.
11. Bassler BL, Losick R. Bacterially speaking. Cell 2006; 125:237-46.
12. Hughes DT, Sperandio V. Inter-kingdom signaling: communication between bacteria and their hosts. Nat Rev Microbiol 2008; 6:111-20.
13. Hellingwerf KJ. Bacterial observations: a rudimentary form of intelligence? Trends Microbiol 2005; 13:152-8.
14. Hellingwerf KJ, Postma PW, Tommassen J, Westerhoff HV. Signal transduction in bacteria: phospho-neural network(s) in *Escherichia coli*? FEMS Microbiol Rev 1995; 16:309-21.
15. Ben Jacob E. Bacterial wisdom, Gödel's theorem and creative genomic webs. Physica A 1998; 248:57-76.
16. Strassmann JE. Bacterial cheaters. Nature 2000; 404:555-6.
17. Velicer GJ, Kroos L, Lenski RE. Developmental cheating in the social bacterium Myxococcus xanthus. Nature 2000; 404:598-601.
18. Armitage JP, Holland IB, Jenal U, Kenny B. 'Neural networks' in bacteria: making connections. J Bacteriol 2005; 187:26-36.
19. Fiegna F, Yu YT, Kadam SV, Velicer GJ. Evolution of an obligate social cheater to a superior cooperator. Nature 2006; 441:310-4.
20. Van Duijn M, Keijzer F, Franken D. Principles of minimal cognition: casting cognition as sensorimotor coordination. Adapt Behav 2006; 14:157-70.
21. Falkner R, Priewasser M, Falkner G. Information processing by cyanobacteria during adaptation to environmental phosphate fluctuations. Plant Signal Behav 2006; 1:212-20.
22. Tasneem A, Iyer LM, Jakobsson E, Aravind L. Identification of the prokaryotic ligand-gated ion channels and their implications for the mechanisms and origins of animal Cys-loop ion channels.Genome Biol 2005; 6:R4.
23. Bocquet N, Prado de Carvalho L, Cartaud J, Neyton J, Le Poupon C, Taly A, Grutter T, Changeux JP, Corringer PJ. A prokaryotic proton-gated ion channel from the nicotinic acetylcholine receptor family. Nature 2007; 445:116-9.
24. Pechère JC. How bacteria resist antibiotics: a primary form of collective intelligence? Bull Acad Natl Med 2004; 188:1249-56.
25. Pechère JC. The Intelligent Microbe. Frison-Roche, 2007.
26. Greenspan RJ. An Introduction to Nervous Systems. Cold Spring Harbor Laboratory Press, 2007.
27. Sineshchekov OA, Govorunova EG. Rhodopsin-mediated photosensing in green flagellated algae. Trends Plant Sci 1999; 4:58-63.
28. Kateriya S, Nagel G, Bamberg E, Hegemann P. 'Vision' in single-celled algae. News Physiol Sci 2004; 19:133-7.
29. Nakagaki T. Smart behavior of true slime mold in a labyrinth. Res Microbiol 2001; 152:767-70.
30. Nakagaki T, Yamada H, Tóth A. Maze-solving by an amoeboid organism. Nature 2000; 407:470.
31. Nakagaki T, Yamada H, Tóth A. Path finding by tube morphogenesis in an amoeboid organism. Biophys Chem 2001; 92:47-52.
32. Nakagaki T, Yamada H, Hara M. Smart network solutions in an amoeboid organism. Biophys Chem 2004; 107:1-5.
33. Nakagaki T, Iima M, Ueda T, Nishiura Y, Saigusa T, Tero A, Kobayashi R, Showalter K. Minimum-risk path finding by an adaptive amoebal network. Phys Rev Lett 2007; 99:068104.
34. Ball P. Cellular memory hints at the origins of intelligence. Nature 2008; 451:385.
35. Saigusa T, Tero A, Nakagaki T, Kuramoto Y. Amoebae anticipate periodic events. Phys Rev Lett 2008; 100:018101.
36. Eusebi F, Oasetto N, Siracusa G. Acetylcholine receptors in human oocytes. J Physiol 1984; 346:321-30.
37. Bray C, Son J-H, Meizel S. A nicotinic acetylcholine receptor is involved in the acrosome reaction of human sperm initiated by recombinant human ZP3. Biol Repr 2002; 67:782-8.
38. Hu JH, Yang N, Ma YH, Jiang J, Zhang JF, Fei J, Guo LH. Identification of glutamate receptors and transporters in mouse and human sperm. J Andr 2004; 25:140-6.
39. Bray C, Son J-H, Meizel S. Acetylcholine causes an increase of intracellular calcium in human sperm. Mol Hum Repr 2005; 11:881-889.
40. Kumar P, Meizel S. Nicotinic acetylcholine receptor subunits and associated proteins in human sperm. J Biol Chem 2005; 280: 25928-35.
41. Bray C, Son J-H, Kumar P, Meizel S. Mice deficient in CHRNA7, a subunit of the nicotinic acetylcholine receptor, produce sperm with impaired motility. Biol Repr 2005; 73:807-14.
42. Corrigan C, Subramanian R, Miller MA. Eph and NMDA receptors control Ca2+/calmodulin-dependent protein kinase II activation during *C. elegans* oocyte meiotic maturation. Development 2005; 132:5225-37.
43. Albrizio M, Guaricci AC, Maritato F, Sciorsci RF, Mari G, Calamita G, Lacalandra GM, Aiudi GG, Minoia R, Dell'Aquila MD, Minoia P. Expression and subcellular localization of the μ-opioid receptor in equine spermatozoa: Evidence for its functional role. Reproduction 2005; 129:39-49.
44. Chen W-Y, Ni Y, Pan Y-N, Shi Q-X, Yuan YY, Chen AJ, Mao LZ, Yu SQ, Roldan ERS. GABA, progesterone and zona pellucida activation of PLA2 and regulation by MEK-ERK1/2 during acrosomal exocytosis in guinea pig spermatozoa. FEBS Letts 2005; 579:4692-700.
45. Agirregoitia E, Valdivia A, Carracedo A, Casis L, Gil J, Subiran N, Ochoa C, Irazusta J. Expression and localization of δ-, κ-, and μ-opioid receptors in human spermatozoa and implications for sperm motility. J Clin Endocrin Metabol 2006; 91:4969-75.
46. Rossato M. Endocannabinoids, sperm functions and energy metabolism. Mol Cell Endocr 2008; 286S:31-35.
47. Rossato M, Pagano C, Vettor R. The cannabinoid system and male reproductive functions. J Neuroendocrinol 2008; 20:90-3.
48. Cacciola G, Chioccarelli T, Ricci G, Meccariello R, Fasano S, Pierantoni R, Cobellis G. The endocannabinoid system in vertebrate male reproduction: A comparative overview. Mol Cell Endocr 2008; 286S:24-30.
49. Lopez CI, Belmonte SA, De Blas GA, Mayorga LS. Membrane-permeant Rab3A triggers acrosomal exocytosis in living human sperm. FASEB J 2007; 21:4121-30.
50. Zhao L, Burkin HR, Shi X, Li L, Reim K, Miller DJ. Complexin I is required for mammalian sperm acrosomal exocytosis. Dev Biol 2007; 307:236-44.
51. Roggero CM, De Blas GA, Dai H, Tomes CN, Rizo J, Mayorga LS. Complexin/synaptotagmin interplay controls acrosomal exocytosis. J Biol Chem 2007; 282:26335-43.
52. Tomes CN. Molecular mechanisms of membrane fusion during acrosomal exocytosis. Soc Reprod Fertil 2007; 65:275-91.
53. Baluška F, Volkmann D, Menzel D. Plant synapses: actin-based domains for cell-cell communication. Trends Plant Sci 2005; 10:106-11.
54. Baluška F, Hlavacka A, Mancuso S, Barlow PW. Neurobiological view of plants and their body plan. In: Baluška F, Mancuso S, Volkmann D, eds. Communication in Plants: Neuronal Aspects of Plant Life. New York: Springer Verlag, 2006; 19-35.
55. Brenner ED, Stahlberg R, Mancuso S, Vivanco J, Baluška F, Van Volkenburgh E. Plant neurobiology: an integrated view of plant signaling. Trends Plant Sci 2006; 11:413-9.
56. Calvo Garzón F. The quest for cognition in plant neurobiology. Plant Signal Behav 2007; 2:208-11.
57. Calvo Garzón F, Keijzer F. Cognition in plants. In: Baluška F, ed. Plant-Environment Interactions from Behavioral Perspective. New York: Springer Verlag, 2009; In press.
58. Karban R. Plant behavior and communication. Ecol Lett 2008; 11:727-39.
59. Trewavas A. Aspects of plant intelligence. Ann Bot 2003; 92:1-20.
60. Trewavas A. Plant intelligence. Naturwissenschaften 2005a; 92:401-13.
61. Trewavas A. Green plants as intelligent organisms. Trends Plant Sci *2005b;* 10:413-9.
62. Trewavas A. Response to Alpi et al.: Plant neurobiology—all metaphors have value. Trends Plant Sci 2007; 12:231-3.
63. Felle HH, Zimmermann MR. Systemic signaling in barley through action potentials. Planta 2007; 226:203-14.
64. Fromm J, Lautner S. Electrical signals and their physiological significance in plants. Plant Cell Environ 2007; 30:249-57.
65. Baluška F, Šamaj J, Menzel D. Polar transport of auxin: carrier-mediated flux across the plasma membrane or neurotransmitter-like secretion? 2003; Trends Cell Biol 13:282-5.

66. Baluška F, Šamaj J, Wojtaszek P, Volkmann D, Menzel D. Cytoskeleton—plasma membrane—cell wall continuum in plants: emerging links revisited. Plant Physiol 2003b; 133:482-91.
67. Baluška F, Volkmann D, Barlow PW. A polarity crossroad in the transition growth zone of maize root apices: cytoskeletal and developmental implications. J Plant Growth Regul 2001; 20:170-81.
68. Baluška F, Mancuso S, Volkmann D, Barlow PW. Root apices as plant command centres: the unique 'brain-like' status of the root apex transition zone. Biologia 2004; 59:9-14.
69. Mancuso S, Marras AM, Mugnai S, Schlicht M, Zarsky V, Li G, Song L, Hue HW, Baluška F. Phospholipase Dζ2 drives vesicular secretion of auxin for its polar cell-cell transport in the transition zone of the root apex. Plant Signal Behav 2007; 2:240-4.
70. Verbelen J-P, De Cnodder T, Le J, Vissenberg K, Baluška F. The root apex of Arabidopsis thaliana consists of four distinct zones of cellular activities: meristematic zone, transition zone, fast elongation zone, and growth terminating zone. Plant Signal Behav 2006; 1:296-304.
71. Baluška F, Schlicht M, Volkmann D, Mancuso S. Vesicular secretion of auxin: Evidences and implications. Plant Signal Behav 2008; 3:254-56.
72. Schlicht M. Polar auxin transport and auxin-induced development: root system and signaling molecules give the clue. PhD Thesis 2008; University of Bonn.
73. Schlicht M, Strnad M, Scanlon MJ, Mancuso S, Hochholdinger F, Palme K, Volkmann D, Menzel D, Baluška F. Auxin immunolocalization implicates vesicular neurotransmitter-like mode of polar auxin transport in root apices. Plant Signal Behav 2006; 1:122-33.
74. Masi E, Ciszak M, Stefano G, Renna L, Azzarello E, Pandolfi C, Mugnai S, Baluška F, Arecchi FT, Mancuso S. Spatio-temporal dynamics of the electrical network activity in the root apex: A multi-electrode array (MEA) study. Proc Natl Acad Sci USA 2008; Provisionally Accepted.
75. Ripoll C, Le Sceller L, Verdus MC, Norris V, Tafforeau M, Thellier M. Memorization of abiotic stimuli in plants. A complex role for calcium. In: Baluška F, ed. Plant-Environment Interactions from Behavioral Perspective. New York: Springer Verlag, 2009; In press.
76. Galis I, Gaquerei E, Pandey SP, Baldwin IT. Molecular mechanisms underlying plant memory in JA-mediated defence responses. Plant Cell Environm 2008; In press.
77. Callaway RM, Mahall BE, Plant ecology: family roots. Nature 2007; 448:145-7.
78. Dudley SA, File AL. Kin recognition in an annual plant. Biol Lett 2008; 3:435-8.
79. Alpi A, Amrhein N, Bertl A, Blatt MR, Blumwald E, Cervone F, Dainty J, De Michelis MI, Epstein E, Galston AW, Goldsmith MH, Hawes C, Hell R, Hetherington A, Hofte H, Juergens G, Leaver CJ, Moroni A, Murphy A, Oparka K, Perata P, Quader H, Rausch T, Ritzenthaler C, Rivetta A, Robinson DG, Sanders D, Scheres B, Schumacher K, Sentenac H, Slayman CL, Soave C, Somerville C, Taiz L, Thiel G, Wagner R.Plant neurobiology: no brain, no gain? Trends Plant Sci 2007; 12:135-6.
80. Brenner ED, Stahlberg R, Mancuso S, Vivanco J, Baluška F, Van Volkenburgh E. Response to Alpi et al.: Plant neurobiology—the gain is more than the name. Trends Plant Sci 2007; 12:285-6.
81. Taylor AE. Commnetary on Plato's Timaeus. Oxford, 1972.
82. Ingensiep HW. Geschichte der Pflanzenseele. Stuttgart: Alfred Kröner Verlag, 2001.
83. Darwin CR. (assisted by Darwin F.) The Power of Movements in Plants. London: John Murray, 1880.
84. Baluška F, Mancuso S. Plants and animals: wide comparison. In: Baluška F, ed. Plant-Environment Interactions from Behavioral Perspective. New York: Springer Verlag, 2009; In press.
85. Barlow PW. Charles Darwin and the plant root apex: closing the gap in Living Systems Theory as applied to plants. In: Baluška F, Mancuso S, Volkmann D, eds. Communication in Plants: Neuronal Aspects of Plant Life. New York: Springer Verlag, 2006; 37-51.
86. Barlow PW. Reflections on plant neurobiology. Biosystems 2008; 92:132-47.
87. Meinhardt H. The radial-symmetric Hydra and the evolution of the bilateral body plan: an old body became a young brain. BioEssays 2002; 24:185-91.
88. Meinhardt H. Primary body axes of vertebrates: generation of a near-cartesian coordinate system and the role of Spemann-type organizer. Dev Dynam 2005; 2907-19.
89. Holland ND. Early central nervous system evolution: an era of skin brains? Nat Rev Neurosci 2003; 4:617-27.
90. Smith AB. Deuterostomes in a twist: the origins of a radical new body plan. Evol Dev 2008; 10:493-503.
91. Dawkins R. The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution. Mariner Books, 2005.
92. McCauley DW. Serotonin plays an early role in the metamorphosis of the hydrozoan Phialidium gregarium. Dev Biol 1997; 190:229-40.
93. Zega G, Pennati R, Fanzago A, De Bernardi F. Serotonin involvement in the metamorphosis of the hydroid Eudendrium racemosum. Int J Dev Biol 2007; 51:307-13.
94. Katsukura Y, David CN, Grimmelikhuijzen CJ, Sugiyama T. Inhibition of metamorphosis by RFamide neuropeptides in planula larvae of Hydractinia echinata. Dev Genes Evol. 2003; 213:579-86.
95. Thompson SE, Callow JA, Callow ME, Wheeler GL, Taylor AR, Brownlee C. Membrane recycling and calcium dynamics during settlement and adhesion of zoospores of the green alga Ulva linza. Plant Cell Environ 2007; 30:733-44.
96. Ackland JC, West JA, Pickett-Heaps J. Actin and myosin regulate pseudopodia of Porphyra pulchella (Rhodophyta) archeospores. J Phycol 2007; 43:129-38.
97. Li L, Saga N, Mikami K. Phosphatidylinositol 3-kinase activity and asymmetrical accumulation of F-actin are necessary for establishment of cell polarity in the early development of monospores from the marine red alga Porphyra yezoensis. J Exp Bot 2008; 59: 3575-86.
98. Kortschak RD, Samuel G, Saint R, Miller DJ. EST analysis of the cnidarian Acropora millepora reveals extensive gene loss and rapid sequence divergence in the model invertebrates. Curr Biol 2003; 13:2190-5.
99. Technau U, Rudd S, Maxwell P, Gordon PM, Saina M, Grasso LC et al. Maintenance of ancestral complexity and non-metazoan genes in two basal cnidarians. Trends Genet 2005; 21:633-9.
100. Burke RD, Angerer LM, Elphick MR, Humphrey GW, Yaguchi S, Kiyama T, Liang S, Mu X, Agca C, Klein WH, Brandhorst BP, Rowe M, Wilson K, Churcher AM, Taylor JS, Chen N, Murray G, Wang D, Mellott D, Olinski R, Hallböök F, Thorndyke MC. A genomic view of the sea urchin nervous system. Dev Biol 2006; 300:434-60.
101. Materna SC, Cameron RA. The sea urchin genome as a window on function. Dev Biol 2008; 214:266-73.
102. Srivastava M, Begovic E, Chapman J, et al. The Trichoplax genome and the nature of placozoans. Nature 2008; 454:955-60.
103. Pennisi E. 'Simple' animal's genome proves unexpectedly complex. Science 2008; 321:1028-9.
104. Edelman GM. Second Nature. Brian Science and Human Knowledge. New Haven: Yale University Press, 2006.
105. Goldsworthy A. The evolution of plant action potential. J Theor Biol 1983; 103:645-8.
106. Goldsworthy A. The cell electric. New Scientist 1982; 102:14-5.
107. Saha RN, Dudek SM. Action potentials: to the nucleus and beyond. Exp Biol Med 233:385-93.
108. Steinhardt RA, Bi G, Alderton JM. Cell membrane resealing by a vesicular mechanism similar to neurotransmitter release. Science 1994; 263:390-3.
109. Schapire A, Voigt B, Jasik J, Rosado A, Lopez-Cobollo R, Menzel D, Salinas J, Mancuso S, Valpuesta V, Baluška F, Botella MA. Arabidopsis plant synaptotagmin 1 is required for maintenance of plasma membrane integrity and cell viability. Plant Cell 2008; In Press.
110. Sonner JM. A hypothesis on the origin and evolution of the response to inhaled anesthetics. Anesth Analg 2008; 107:849-54.
111. Araki T, Uesono Y, Oguchi T, Toh-EA.LAS24/KOG1, a component of the TOR complex 1 (TORC1), is needed for resistance to local anesthetic tetracaine and normal distribution of actin cytoskeleton in yeast.Genes Genet Syst 2005; 80:325-43.
112. Uesono Y, Araki T, Toh-EA. Local anesthetics, antipsychotic phenothiazines, and cationic surfactants shut down intracellular reactions through membrane perturbation in yeast. Biosci Biotechnol Biochem 2008; 72:2884-94.
113. Kendrick MD, Chang C. Ethylene signaling: new levels of complexity and regulation. Curr Opin Plant Biol 2008; 11:479-85.
114. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003; 348:2110-25.
115. Urban BW, Bleckwenn N. Concepts and correlations relevant to general anaesthesia. Brit J Anasth 2002; 89:3-16.
116. Okazaki N, Takai K, Sato T. Immobilization of a sensitive plant, *Mimosa pudica L.*, by volatile anesthetics. Masui 1993; 42:1190-3.
117. Milne A, Beamish T. Inhalational and local anesthetics reduce tactile and thermal responses in *Mimosa pudica*. Can J Anaesth 1999; 46:287-9.
118. Kovac L. Information and knowledge in biology: Time for reappraisal. Plant Signal Behav 2007; 2:65-73.
119. Kovac L. Bioenergetics—a key to brain and mind. Comm Integr Biol 2008; 1:114-22.
120. Kaufmann S. Reinventing the Sacred. A New View of Science, Reason and Religion. Basic Books, 2008.
121. Beck H, Yaari Y. Plasticity of intrinsic neuronal properties in CNS disorders. Nat Rev Neurosci 2008; 9:357-69.
122. Cohen S, Greenberg ME. Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. Annu Rev Cell Dev Biol 2008; 24:183-209.
123. DeBello WM. Micro-rewiring as a substrate for learning. Trends Neurosci 2008; 31:577-84.
124. Sjöström PJ, Rancz EA, Roth A, Häusser M. Dendritic excitability and synaptic plasticity. Physiol Rev 2008; 88:769-840.
125. Mukhopadhyay S, Lu Y, Shaham S, Sengupta P. Sensory signaling-dependent remodeling of olfactory cilia architecture in *C. elegans*. Dev Cell 2008; 14:762-74.
126. Reiter JF. A cilium is not a cilium: Signaling contributes to ciliary morphological diversity. Dev Cell 2008; 14:635-6.
127. Danchin E, Giraldeau LA, Valone TJ, Wagner RH. Public information: From nosy neighbors to cultural evolution. Science 2004; 305:487-91.
128. Justice SS, Hunstad DA, Cegelski L, Hultgren SJ. Morphological plasticity as a bacterial survival strategy. Nat Rev Microbiol 2008; 6:162-8.
129. Borges RM. Plasticity comparisons between plants and animals: concepts and mechanisms. Plant Signal Behav 2008; 3:367-75.
130. Friml J. Auxin transport—shaping the plant. Curr Opin Plant Biol 2003; 6:7-12.
131. Szentágothai J, Érdi P. Self-organization in the nervous system. J Social Biol Struct 1989; 12:367-84.
132. Baldauf SL, Palmer JD. Animals and fungi are each other's closest relatives: congruent evidence from multiple proteins. Proc Natl Acad Sci USA 1993; 90:11558-62.

133. Stiller JW. Plastid endosymbiosis, genome evolution and the origin of green plants. Trends Plant Sci 2007; 12:391-6.
134. Veerappen CS, Avramova Z, Moriyama EN. Evolution of SET-domain protein families in the unicellular and multicellular Ascomycota fungi. BMC Evol Biol 2008; 8:190.
135. Crivellato E, Ribatti D. A portrait of Aristotle as an anatomist: Historical article. Clin Anat 2007; 20:477-85.
136. Pollan M. The omnivore's next dilemma: Michael Pollan on TED.com. TEDBlock, February 7, 2008; http://blog.ted.com/2008/02/michael_pollan.php
137. Pollan M. The Botany of Desire: A Plant's-Eye View of the World. 2002; Random House.
138. Russo EB, Jiang HE, Li X, Sutton A, Carboni A, del Bianco F, Mandolino G, Potter DJ, Zhao YX, Bera S, Zhang YB, Lü EG, Ferguson DK, Hueber F, Zhao LC, Liu CJ, Wang YF, Li CS. Phytochemical and genetic analyses of ancient cannabis from Central Asia. J Exp Bot 2008; 59:4171-82.
139. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodiv 2007; 4:1614-48.
140. Piccolino M, Wade NJ. Galileo Galilei's vision of senses. Trends Neurosci 2008; 31:585-90.
141. âPiccolino M, Wade NJ. Galileo's eye: a new vision of the senses in the work of Galileo Galilei. Perception 2008; 37:1312-40.