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# Building Complex Brains – Missing Pieces in an Evolutionary Puzzle

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## **Key Words**

Brain size • Complexity • Accelerated evolution • Neurotrophic factor • Microcephaly • Mollusk • Cephalopod

### Abstract

The mechanisms underlying evolution of complex nervous systems are not well understood. In recent years there have been a number of attempts to correlate specific gene families or evolutionary processes with increased brain complexity in the vertebrate lineage. Candidates for evocation of complexity include genes involved in regulating brain size, such as neurotrophic factors or microcephaly-related genes; or wider evolutionary processes, such as accelerated evolution of brain-expressed genes or enhanced RNA splicing or editing events in primates. An inherent weakness of these studies is that they are correlative by nature, and almost exclusively focused on the mammalian and specifically the primate lineage. Another problem with genomic analyses is that it is difficult to identify functionally similar yet non-homologous molecules such as different families of cysteinerich neurotrophic factors in different phyla. As long as comprehensive experimental studies of these questions are not feasible, additional perspectives for evolutionary and genomic studies will be very helpful. Cephalopod mollusks

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Accessible online at: www.karger.com/bbe represent the most complex nervous systems outside the vertebrate lineage, thus we suggest that genome sequencing of different mollusk models will provide useful insights into the evolution of complex brains.

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#### Introduction

The evolutionary mechanisms underlying the generation of complex nervous systems are a topic of keen interest to both scientists and the general public, especially when the discussion touches upon the differences (or lack thereof) between humans and other primates. A difficulty in this debate is that complexity is much easier to recognize than to define. Most (although perhaps not all) researchers would agree that their political leaders have more complex brains than their house pets, however a rigorous quantitative definition of nervous system complexity is not yet available. Much of the debate on this issue can be categorized under the heading 'Does size matter?', but there is no clear consensus on whether one should give weight to absolute brain size (in which case humans do not compare favorably to elephants), relative brain size (in which case shrews clearly outrank humans), or measures such as the encephalization quotient (see below), wherein humans come out ahead, but other primates do not line up according to subjective perceptions of their relative intelligence [Roth and Dicke, 2005]. Dif-

Dr. Mike Fainzilber Department of Biological Chemistry Weizmann Institute of Science IL–76100 Rehovot (Israel) Tel. +972 8 934 4266, Fax +972 8 934 4112, E-Mail mike.fainzilber@weizmann.ac.il ferent authors have suggested various measures of information-processing capacity as surrogates for estimation of complexity, such as neuronal number factored with synapse number and type [Jaaro et al., 2001]; or the encephalization quotient, defined as the number of cortical neurons factored with average nerve conduction velocities [Roth and Dicke, 2005]. None of the proposed options gives a satisfactory estimation available throughout the animal kingdom, but regardless of which surrogate one prefers, much of the focus on evolutionary complexity of neuronal systems has been on factors or genes that influence neuronal numbers or brain size.

## Regulation of Neuronal Numbers: Roles of Neurotrophic Factors

One of the primary mechanisms for the regulation of neuronal numbers is regulation of neuronal survival by neurotrophic factors, most prominently the nerve growth factor family of neurotrophins [Huang and Reichardt, 2003; Glebova and Ginty, 2005]. Although neurotrophins have been found throughout the vertebrate lineage [Hallböök, 1999; Hallböök et al., 2006; von Bartheld and Fritzsch, 2006] and none of their known properties would predict their existence only in vertebrates [Barde, 1994], neurotrophin homologuess were not identified in first drafts of the C. elegans or Drosophila genome sequences [Chao, 2000; Jaaro et al., 2001]. However, the recent expansion of genome sequences and cloning efforts have facilitated the identification of neurotrophins and/or their trk or p75 receptors in a number of invertebrate phyla [van Kesteren et al., 1998; Beck et al., 2004; Ormond et al., 2004; Benito-Gutierrez et al., 2005; Bothwell, 2006]. Interestingly, the extracellular ligand-binding domains of trk family members have strikingly diverged in different phyla, leading to the suggestion that an important driving force for divergence of receptors is the ease of divergence of their ligands [Sossin, 2006]. For example Cysteine Rich Neurotrophic Factor (CRNF) is the only validated p75 ligand found to date in mollusks [Fainzilber et al., 1996], yet its sequence is not similar to that of the neurotrophins. Nonetheless, like the neurotrophins, CRNF forms a non-covalent dimer in solution, and acts as a survival and outgrowth factor for its target neurons [Jaaro, 2004]. The cysteine scaffold of CRNF shares some similarities to that of TCEN49, a neurotrophic factor from a freshwater planarian [Bueno et al., 2002], as well as to various cysteine-rich peptides involved in innate immunity or prey intoxication mechanisms in other invertebrate phyla [Jaaro, 2004]. In addition to CRNF, Epidermal Growth Factor (EGF) superfamily members can act as trophic factors in invertebrates [Hermann et al., 2000; Beck and Fainzilber, 2002; Hidalgo, 2002; Hidalgo et al., 2006]. Thus, although early workers thought that neuronal survival was primarily regulated by neurotrophins, diverse families of molecules can fulfill this role in invertebrate phyla. Furthermore, recent work in mammalian models has shown that Transforming Growth Factor  $\beta$ (TGFβ) superfamily members control or modulate survival of certain neuron subpopulations [Peterziel et al., 2002; Eketjall et al., 2004; Airaksinen et al., 2006], and that proteins originally characterized as axon guidance molecules can regulate the survival of neuronal progenitors [Depaepe et al., 2005] or developing neurons [Ben-Zvi et al., 2006]. One is left therefore with the disconcerting conclusion that even if one can sequence every single base pair of an organism's genome, functional studies will still be required for definitive conclusions on the importance of neurotrophic mechanisms in sculpting its nervous system.

## **Other Factors Controlling Brain Size**

If secreted growth factors and their receptors are not easily linked to the increased capacity of an organism to develop brain complexities that endow it with the capacity to watch daytime television (for example), what about other factors that control brain size? Single gene mutations or deletions can have profound effects on forebrain or cortex size due to shortening of the cell cycle, thus leading to premature differentiation of neuronal precursors [Martynoga et al., 2005; Lien et al., 2006]. Mutations in at least six human genes have been associated with severe forms of small head size (congenital microcephaly) [Gilbert et al., 2005], apparently due to their roles in controlling the assembly and orientation of the mitotic spindle in neuronal precursors, thus indirectly controlling precursor cell numbers and cortex size [Bond and Woods, 2006]. Evolutionary studies on these genes have suggested that three of them reveal molecular signatures for accelerated evolution in the human lineage [Gilbert et al., 2005; Ponting and Jackson, 2005]. The most comprehensive studies were carried out on the ASPM (Abnormal Spindle-like Microcephaly-associated) gene, and show that although most of the ASPM sequence is highly conserved, specific segments reveal high Dn/Ds ratios [Zhang, 2003; Evans et al., 2004]. Dn/Ds is defined as the ratio of nonsynonymous mutations (Dn, reflecting muta-

tions in DNA that cause an amino acid change in an encoded protein) to synonymous mutations (Ds, reflecting mutations in DNA that do not change the sequence of the encoded protein). A high Dn/Ds ratio is one feature thought to be consistent with strong positive selection for evolutionary change. This criterion suggests that the ASPM gene sequence underwent accelerated evolution in the African hominoid clade, preceding hominid brain expansion by several million years [Kouprina et al., 2004]. These and other studies have lead to the proposition that accelerated evolution of microcephaly-associated genes was important for the evolution of increased brain size in humans [Gilbert et al., 2005; Ponting and Jackson, 2005]. It is difficult however to judge the broad relevance of a hypothesis based solely on correlations. Moreover, the relationship between brain size and cognitive capacity is not necessarily straightforward. The intracranial volume of Homo floresiensis, a fossil dwarf hominid recently described from Indonesia, is comparable to that of microcephalic individuals of Homo sapiens, yet the H. floresiensis brain had relatively large temporal lobes and highly folded and convoluted frontal lobes [Falk et al., 2005]. These areas of the brain are implicated in higher cognitive functions, and more recent fossil evidence suggests that H. floresiensis engaged in sophisticated behavior including use of fire and cooperative hunting [Morwood et al., 2005].

Claims for accelerated evolution leading to increased brain capacity in hominids are not limited to microcephaly-associated genes and brain size. An initial analysis of Dn/Ds ratios in 200 nervous system genes did not find high absolute values, but as the values for primates were higher than for rodents, the authors took them as evidence for positive selection in genes implicated in nervous system development in the primate lineage [Dorus et al., 2004]. Subsequent genome-wide primate studies did not find a higher preponderance of positively selected genes in the nervous system as compared to other tissues, although a small fraction of nervous system genes clearly exhibit high Dn/Ds ratios [Khaitovich et al., 2005b; Nielsen et al., 2005]. This discrepancy can be rationalized if a small subset of neural genes are positively selected, whereas most are targets of strong purifying selection due to the fitness cost of deleterious mutations in brain function [Hill and Walsh, 2005]. It should also be noted that a high Dn/Ds value can arise in a data-set with skewed amino acid composition or unusual transitiontransversion ratios, thus it cannot be used definitively as sole proof of positive selection [Dagan et al., 2002]. Even if positive selection is widespread in nervous system

genes, the notion that this drives human brain evolution must now contend with the fact that there is actually stronger evidence for positive selection in testis-specific genes than in those associated with the nervous system [Nielsen et al., 2005].

In addition to positive Darwinian selection, other evolutionary processes such as RNA editing, differential splicing, or modified gene expression might all correlate with increased brainpower in the human lineage [see e.g., Hoopengardner et al., 2003; Herbert, 2004; Khaitovich et al., 2005a; Levanon et al., 2005]. As with other factors detailed above, the evidence for involvement of the latter processes in the evolution of complexity in the nervous system is correlative only, and in some cases tinged with a healthy dose of wishful thinking. Because direct experimental testing of hypotheses of brain evolution is not yet possible, new perspectives from evolutionary genomics on additional organisms will be very helpful. The question then becomes where can one find such a perspective? Although there could be some utility in assessments of adjacent twigs on the evolutionary tree, such as cetaceans [Hof et al., 2005], fundamental insights in comparative genomics often arise from information derived from distant relatives, and the more distant the better [see e.g., Koonin, 2000; Koonin et al., 2004]. We would like to argue that comparative genomics on mollusk models offer the best chances for such insights on the question at hand, as cephalopod mollusks represent the most complex nervous systems outside the vertebrate lineage.

## Octopus and Squid: More than Just a Dinner

The Cephalopoda are an ancient group of mollusks originating in the late Cambrian. Ancestors of modern coleoid cephalopods (octopus and squid) diverged from the externally-shelled nautiloids in the Ordovician, with approximately 600 million years of separate evolution between the cephalopod and the vertebrate lineages. The evolution of modern coleoids has been strongly influenced by competition and predatory pressures from fish, to a degree that the behavior of squid and octopus are more akin to that of fast-moving aquatic vertebrates than to other mollusks [Hanlon and Messenger, 1996; Boyle, 2000]. Squid and octopuses are agile and active animals with sophisticated sensory and motor capabilities. Their central nervous systems are much larger than those of other mollusks, with the main ganglia fused into a brain that surrounds the esophagus with additional lateral optic lobes. The number of neurons in an adult cephalopod

brain can reach 200 million [Giuditta et al., 1971], approximately four orders of magnitude higher than the 20-30,000 neurons found in model mollusks such as Aplysia or Lymnaea. Cephalopods exhibit sophisticated behaviors [Hanlon and Messenger, 1996; Boyle, 2000; Cole and Adamo, 2005] and a number of studies have presented evidence for diverse modes of learning and memory in Octopus and cuttlefish models [Fiorito and Scotto, 1992; Robertson et al., 1996; Moriyama and Gunji, 1997; Boal et al., 2000; Dickel et al., 2001]. This learning capacity is reflected in a sophisticated circuitry of neural networks in the cephalopod nervous system [Budelmann, 1995; Williamson and Chrachri, 2004]. Moreover, electrophysiological studies have revealed vertebrate-like properties in the cephalopod brain, such as compound field potentials [Bullock and Budelmann, 1991; Budelmann, 1995] and long-term potentiation [Hochner et al., 2003]. Thus cephalopods exhibit all the attributes of complex nervous systems on the anatomical, cellular, functional and behavioral levels. The American National Human Genome

Research Institute (NHGRI) recently announced a commitment to fund a ten-fold coverage draft sequence of the genome of Aplysia californica (see www.genome.gov/ 13014443). This effort will provide a reference mollusk genome sequence for a model with a nervous system comprising 25,000 neurons. A parallel effort on a well-studied octopus or squid should provide insights on the evolutionary processes that allowed development of the sophisticated cephalopod nervous system. For example, have cephalopods undergone accelerated evolution in specific nervous system genes, as has been suggested for primates? Have specific gene families undergone expansion in the cephalopod lineage and are these expressed in the nervous system? Are there clear parallels in accelerated evolution, gene family expansion, and other evolutionary processes between cephalopods and vertebrates? Answers to these and related questions will provide useful perspectives for evaluation of the processes thought to be involved in the evolution of the vertebrate brain.

#### References

- Airaksinen MS, Hatinen T, Holm L (2006) Evolution of the GDNF family ligands and receptors. Brain Behav Evol 68:181–190.
- Barde YA (1994) Neurotrophic factors: an evolutionary perspective. J Neurobiol 25:1329– 1333.
- Beck G, Fainzilber M (2002) Genetic models meet trophic mechanisms: EGF family members are gliatrophins in Drosophila. Neuron 33:673–675.
- Beck G, Munno DW, Levy Z, Dissel HM, Van-Minnen J, Syed NI, Fainzilber M (2004) Neurotrophic activities of trk receptors conserved over 600 million years of evolution. J Neurobiol 60:12–20.
- Ben-Zvi A, Yagil Z, Hagalili Y, Klein H, Lerman O, Behar O (2006) Semaphorin 3A and neurotrophins: a balance between apoptosis and survival signaling in embryonic DRG neurons. J Neurochem 96:585–597.
- Benito-Gutierrez E, Nake C, Llovera M, Comella JX, Garcia-Fernandez J (2005) The single AmphiTrk receptor highlights increased complexity of neurotrophin signalling in vertebrates and suggests an early role in developing sensory neuroepidermal cells. Development 132:2191–2202.
- Boal JG, Dunham AW, Williams KT, Hanlon RT (2000) Experimental evidence for spatial learning in octopuses (octopus bimaculoides). J Comp Psychol 114:246–252.

- Bond J, Woods CG (2006) Cytoskeletal genes regulating brain size. Curr Opin Cell Biol 18: 95–101.
- Bothwell M (2006) Evolution of the neurotrophin signaling system in invertebrates. Brain Behav Evol 68:124–132.
- Boyle P (2000) Fast and flexible: the cephalopod repertoire. Biologist (London) 47:171–175.
- Budelmann BU (1995) The cephalopod nervous system: What evolution has made of the molluscan design. In: The Nervous Systems of Invertebrates: An Evolutionary and Comparative Approach (Breidbach O, Kutsch W, eds), pp 115–138. Basel: Birkhäuser Verlag.
- Bueno D, Fernandez-Rodriguez J, Cardona A, Hernandez-Hernandez V, Romero R (2002) A novel invertebrate trophic factor related to invertebrate neurotrophins is involved in planarian body regional survival and asexual reproduction. Dev Biol 252:188–201.
- Bullock TH, Budelmann BU (1991) Sensory evoked potentials in unanesthetized unrestrained cuttlefish: a new preparation for brain physiology in cephalopods. J Comp Physiol A 168:141–150.
- Chao MV (2000) Trophic factors: An evolutionary cul-de-sac or door into higher neuronal function? J Neurosci Res 59:353–355.
- Cole PD, Adamo SA (2005) Cuttlefish (Sepia officinalis: Cephalopoda) hunting behavior and associative learning. Anim Cogn 8:27– 30.

- Dagan T, Talmor Y, Graur D (2002) Ratios of radical to conservative amino acid replacement are affected by mutational and compositional factors and may not be indicative of positive Darwinian selection. Mol Biol Evol 19:1022–1025.
- Depaepe V, Suarez-Gonzalez N, Dufour A, Passante L, Gorski JA, Jones KR, Ledent C, Vanderhaeghen P (2005) Ephrin signalling controls brain size by regulating apoptosis of neural progenitors. Nature 435:1244–1250.
- Dickel L, Chichery MP, Chichery R (2001) Increase of learning abilities and maturation of the vertical lobe complex during postembryonic development in the cuttlefish, Sepia. Dev Psychobiol 39:92–98.
- Dorus S, Vallender EJ, Evans PD, Anderson JR, Gilbert SL, Mahowald M, Wyckoff GJ, Malcom CM, Lahn BT (2004) Accelerated evolution of nervous system genes in the origin of *Homo sapiens*. Cell 119:1027–1040.
- Eketjall S, Jornvall H, Lonnerberg P, Kobayashi S, Ibáñez CF (2004) Recent evolutionary origin within the primate lineage of two pseudogenes with similarity to members of the transforming growth factor-beta superfamily. Cell Mol Life Sci 61:488–496.
- Evans PD, Anderson JR, Vallender EJ, Gilbert SL, Malcom CM, Dorus S, Lahn BT (2004) Adaptive evolution of ASPM, a major determinant of cerebral cortical size in humans. Hum Mol Genet 13:489–494.

- Fainzilber M, Smit AB, Syed NI, Wildering WC, Hermann, van der Schors RC, Jimenez C, Li KW, van Minnen J, Bulloch AG, Ibáñez CF, Geraerts WP (1996) CRNF, a molluscan neurotrophic factor that interacts with the p75 neurotrophin receptor. Science 274:1540– 1543.
- Falk D, Hildebolt C, Smith K, Morwood MJ, Sutikna T, Brown P, Jatmiko E, Saptomo EW, Brunsden B, Prior F (2005) The brain of LB1, *Homo floresiensis*. Science 308:242–245.
- Fiorito G, Scotto P (1992) Observational learning in *Octopus vulgaris*. Science 256:545– 547.
- Gilbert SL, Dobyns WB, Lahn BT (2005) Genetic links between brain development and brain evolution. Nat Rev Genet 6:581–590.
- Giuditta A, Libonati M, Packard A, Prozzo N (1971) Nuclear counts in the brain lobes of *Octopus vulgaris* as a function of body size. Brain Res 25:55–62.
- Glebova NO, Ginty DD (2005) Growth and survival signals controlling sympathetic nervous system development. Ann Rev Neurosci 28:191–222.
- Hallböök F (1999) Evolution of the vertebrate neurotrophin and Trk receptor gene families. Curr Opin Neurobiol 9:616–621.
- Hallböök F, Wilson K, Thorndyke M, Olinski RP (2006) Evolution of the neurotrophin and Trk gene families in chordates. Brain Behav Evol 68:133–144.
- Hanlon RT, Messenger JB (1996) Cephalopod Behaviour. Cambridge UK: Cambridge University Press.
- Herbert Å (2004) The four Rs of RNA-directed evolution. Nat Genet 36:19–25.
- Hermann PM, van Kesteren RE, Wildering WC, Painter SD, Reno JM, Smith JS, Kumar SB, Geraerts WP, Ericsson LH, Smit AB, Bulloch AG, Nagle GT (2000) Neurotrophic actions of a novel molluscan epidermal growth factor. J Neurosci 20:6355–6364.
- Hidalgo A (2002) Interactive nervous system development: control of cell survival in *Drosophila*. Trends Neurosci 25:365–370.
- Hidalgo A, Learte AR, McQuilton P, Pennack J, Zhu B (2006) Neurotrophic and gliatrophic contexts in *Drosophila*. Brain Behav Evol 68:173–180.
- Hill RS, Walsh CA (2005) Molecular insights into human brain evolution. Nature 437:64– 67.
- Hochner B, Brown ER, Langella M, Shomrat T, Fiorito G (2003) A learning and memory area in the octopus brain manifests a vertebrate-like long-term potentiation. J Neurophysiol 90:3547–3554.

- Hof PR, Chanis R, Marino L (2005) Cortical complexity in cetacean brains. Anat Rec A Discov Mol Cell Evol Biol 287:1142–1152.
- Hoopengardner B, Bhalla T, Staber C, Reenan R (2003) Nervous system targets of RNA editing identified by comparative genomics. Science 301:832–836.
- Huang EJ, Reichardt LF (2003) Trk receptors: roles in neuronal signal transduction. Ann Rev Biochem 72:609–642.
- Jaaro H (2004) CRNF and other p75 ligands. Ph.D. Thesis, Weizmann Institute of Science, Rehovot, Israel.
- Jaaro H, Beck G, Conticello SG, Fainzilber M (2001) Evolving better brains: a need for neurotrophins? Trends Neurosci 24:79–85.
- Khaitovich P, Hellmann I, Enard W, Nowick K, Leinweber M, Franz H, Weiss G, Lachmann M, Paabo S (2005a) Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. Science 309: 1850–1854.
- Khaitovich P, Paabo S, Weiss G (2005b) Toward a neutral evolutionary model of gene expression. Genetics 170:929–939.
- Koonin EV (2000) How many genes can make a cell: the minimal-gene-set concept. Ann Rev Genomics Hum Genet 1:99–116.
- Koonin EV, Fedorova ND, Jackson JD, Jacobs AR, Krylov DM, Makarova KS, Mazumder R, Mekhedov SL, Nikolskaya AN, Rao BS, Rogozin IB, Smirnov S, Sorokin AV, Sverdlov AV, Vasudevan S, Wolf YI, Yin JJ, Natale DA (2004) A comprehensive evolutionary classification of proteins encoded in complete eukaryotic genomes. Genome Biol 5:R7.
- Kouprina N, Pavlicek A, Mochida GH, Solomon G, Gersch W, Yoon YH, Collura R, Ruvolo M, Barrett JC, Woods CG, Walsh CA, Jurka J, Larionov V (2004) Accelerated evolution of the ASPM gene controlling brain size begins prior to human brain expansion. PLoS Biol 2:E126.
- Levanon K, Eisenberg E, Rechavi G, Levanon EY (2005) Adenosine-to-inosine RNA editing in Alu repeats in the human genome. EMBO Rep 6:831-835.
- Lien WH, Kiezovitch O, Fernandez TE, Delrow J, Vasioukhin V (2006) AlphaE-Catenin controls cerebral cortical size by regulating the Hedgehog signaling pathway. Science 311:1609–1612.
- Martynoga B, Morrison H, Price DJ, Mason JO (2005) Foxg1 is required for specification of ventral telencephalon and region-specific regulation of dorsal telencephalic precursor proliferation and apoptosis. Dev Biol 283: 113–127.

- Moriyama T, Gunji YP (1997) Autonomous learning in maze solution by Octopus. Ethology 103:499–513.
- Morwood MJ, Brown P, Jatmiko, Sutikna T, Saptomo EW, Westaway KE, Due RA, Roberts RG, Maeda T, Wasisto S, Djubiantono T (2005) Further evidence for small-bodied hominids from the Late Pleistocene of Flores, Indonesia. Nature 437:1012–1017.
- Nielsen R, Bustamante C, Clark AG, Glanowski S, Sackton TB, Hubisz MJ, Fledel-Alon A, Tanenbaum DM, Civello D, White TJ, J JS, Adams MD, Cargill M (2005) A scan for positively selected genes in the genomes of humans and chimpanzees. PLoS Biol 3:e170.
- Ormond J, Hislop J, Zhao Y, Webb N, Vaillaincourt F, Dyer JR, Ferraro G, Barker P, Martin KC, Sossin WS (2004) ApTrkl, a Trk-like receptor, mediates serotonin- dependent ERK activation and long-term facilitation in Aplysia sensory neurons. Neuron 44:715–728.
- Peterziel H, Unsicker K, Krieglstein K (2002) TGFbeta induces GDNF responsiveness in neurons by recruitment of GFRalpha1 to the plasma membrane. J Cell Biol 159:157–167.
- Ponting C, Jackson AP (2005) Evolution of primary microcephaly genes and the enlargement of primate brains. Curr Opin Genet Dev 15:241–248.
- Robertson JD, Bonaventura J, Kohm A, Hiscat M (1996) Nitric oxide is necessary for visual learning in *Octopus vulgaris*. Proc Biol Sci 263:1739–1743.
- Roth G, Dicke U (2005) Evolution of the brain and intelligence. Trends Cogn Sci 9:250– 257.
- Sossin WS (2006) Tracing the evolution and function of the Trk superfamily of receptor tyrosine kinases. Brain Behav Evol 68:145– 156.
- van Kesteren RE, Fainzilber M, Hauser G, van Minnen J, Vreugdenhil E, Smit AB, Ibáñez CF, Geraerts WP, Bulloch AG (1998) Early evolutionary origin of the neurotrophin receptor family. EMBO J 17:2534–2542.
- von Bartheld CS, Fritzsch B (2006) Neurotrophin receptors in neuronal populations among vertebrates: tools for evolutionary change or stability in neural circuits? Brain Behav Evol 68:157–172.
- Williamson R, Chrachri A (2004) Cephalopod neural networks. Neurosignals 13:87–98.
- Zhang J (2003) Evolution of the human ASPM gene, a major determinant of brain size. Genetics 165:2063–2070.