ACS Chemical Neuroscience

Viewpoint

pubs.acs.org/chemneuro

The Molecular Basis of Memory

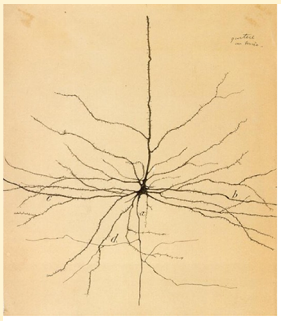
Gerard Marx*

MX Biotech Ltd., Jerusalem, Israel

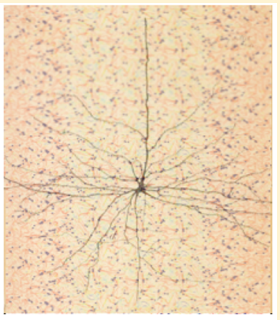
Chaim Gilon*

Institute of Chemistry, Hebrew University, Jerusalem, Israel

ABSTRACT: We propose a *tripartite* biochemical mechanism for memory. Three physiologic components are involved, namely, the neuron (individual and circuit), the surrounding neural extracellular matrix, and the various trace metals distributed within the matrix. The binding of a metal cation affects a corresponding nanostructure (shrinking, twisting, expansion) and dielectric sensibility of the chelating node (address) within the matrix lattice, sensed by the neuron. The neural extracellular matrix serves as an electro-elastic lattice, wherein neurons manipulate multiple trace metals ($n > 10$) to encode, store, and decode coginive information. The proposed mechanism explains brains low energy requirements and high rates of storage capacity described in multiples of Avogadro number ($N_A = 6 \times 10^{23}$). Supportive evidence correlates memory loss to trace metal toxicity or deficiency, or breakdown in the delivery/transport of metals to the matrix, or its degradation. Inherited diseases revolving around dysfunctional trace metal metabolism and memory dysfunction, include Alzheimer's disease (Al, Zn, Fe), Wilson's disease (Cu), thalassemia (Fe), and autism (metallothionein). The *tripartite* mechanism points to the electro-elastic interactions of neurons with trace metals distributed within the neural extracellular matrix, as the molecular underpinning of "synaptic plasticity" affecting short-term memory, long-term memory, and forgetting.



Cajal's naked neuron



Cajal's neuron imbedded in the [nECM/metal] array

KEYWORDS: *Memory, information, ionic chip, neuron, extracellular matrix, trace metal*

BACKGROUND

Biologic memory in the brain is a mystery. Various adjectives have been used to describe memory (i.e., active, declarative, passive, associative, short-term (STM), long-term (LTM), super memory), but none in molecular terms. No consensus exists for how cognitive information (cog-info) is encoded or stored in the brain.

Scientists from disparate disciplines have suggested various molecular mechanism, such as DNA/RNA-based processes, to describe memory. Neuroscientists proposed neural firing patterns, neurocircuits, neural-networks, neurotransmittors, and synaptic firing as the basis for encoding sensory perceptions as memory.[1−22] The "synaptic plasticity" model is unsatisfactory from the perspective of compactness, kinetics, energy requirements, and lack of an information theory.[21] What is missing is a physiologically relevant, molecular mechanism, whereby cog-info derived from the senses can be encoded, stored, and recalled by the neural system.

In computer ionic memory chips,[23−38] information is received, processed, and stored by manipulating the distribution of elemental cations (dopants) within the chip matrix, usually solid electrolytes (metal sulfides, Ge-based chalcogenides, or oxides such as TaO_3, WO_3, SiO_2, TiO_2). Ionic memory chips are doped with Ag, Cu, and Zn . The information theories and binary value (0, 1) algorithms developed by von Neumann, Turing, Weiner, and Shannon are used to encode digital information in the memory chip.[39−49]

Neural Memory Traits. The ionic memory chip is a compelling model for how one would like to describe biological memory in the brain. The characteristics and traits that one wishes to describe include the following:

a) A credible mechanism for memory, based on generally accepted biochemical principles, with available physiologic components.
b) Molecular-scale encoding/decoding process, faster than the rate of neural firing (<100 ms).
c) Large storage capacity for physically encoding cog-info.
d) Low energy requirements (<400 cal/day).
e) Capacity for storing cog-info for short and long durations (recall: 1 min to >1 day).
f) Capable of acquiring (learning), storing, and losing (forgetting) cog-info.
g) Applicable to all animals with neural circuitry.

Received: July 15, 2012
Accepted: July 17, 2012
Published: August 15, 2012

Hypothesis: The *Tripartite* Mechanism of Memory. We propose that "memory" emerges from the dynamic interaction of three physiologic compartments, consisting of the following:

1) Neurons.
2) Neural extracellular matrix (nECM) around the neuron.
3) Trace metal cations dispersed within the nECM (dopants).

The nECM constitutes a hydrated lattice wherein cog-info is encoded, processed, and stored. The neurons manipulate and electro-elastically sense the surrounding ensembles of [nECM/metal] complexes, to encode and recall memory. More specific descriptions of these compartments follow.

1. Neuron.[50−84] The neuron and neural circuits, the computational components of the brain, operate by electrical signaling within an aqueous environment. The cells are intimately connected to the external nECM by electrically sensitive surface features, notably integrin receptors, gap junctions, nodes of Ranvier, and synapses. The electro-elastic contact between the neural surface and its external environment (nECM) is the keystone to neural computation.

2. nECM.[85−135] The nECM surrounding the neurons comprises 20−25% of the total brain volume. It exhibits gross- and microanisotropies in terms of ultrastructure, composition, and dielectric properties. It comprises a block copolymer lattice around the neuron, composed of polymeric glycosaminoglycans (GAG) (hyaluronic acid (HA), lecticans, proteoglycans, chondroitin sulfates (Chon), heparan sulfate (Hep)), which present many anionic/Lewis base moieties for attaching metal cations. Interspersed within the GAG lattice are also many proteins (e.g., collagens, integrins, tenascins, phosphacan, various enzymes) and glycoproteins (e.g., nidogen, reelin, TNC, thrombospondin).

The nECM lattice is an electroelastic hydrogel, characterized by viscoelastic traits, carrying currents on the order of 200 nAmp, with conduction velocities 2−10 m/s, accommodating voltage changes exerted at neuronal synapses and other anatomical sites (i.e., gap junctions, nodes of Ranvier).

We propose that the complexation of a metal cation to specific chelating groups (nodes) within the nECM concomitantly modulates the nanoscale structural, viscoelastic, and dielectric properties of the lattice, sensed by the neuron.

Thus, the nECM serves two functions:

- As the structural scaffolding encasing the neurons, through which gases (oxygen and carbon dioxide), metals, and metabolites diffuse.
- As an electro-elastic lattice used by the neuron to encode and decode cog-info, by modulating or sensing the pattern of metal cations bound to specific nodes (addresses).

3. Trace Metals in the Brain.[136−153] Brain levels of more than 15 trace metals have been measured within the gross tissue as well as within the individual neurons. Metal levels were highest within the neuron, but were present in the nECM, at levels ranging from 10^{-6} to 10^{-9} M (Table 1). Table 1 shows the composition of total human brain tissue, presenting the 15 most prevalent elemental metals. Most (>90%) are sequestered within the neurons, with <10% found in the nECM. The distribution of trace metals is not homogeneous between and within anatomical regions of the brain.

nECM/Metal Complexes: Conformations, Kinetics, and Energetics.[154−165] Parameters, such as metal chelate dissociation constant (K_d), solubility constants of salts (K_{sp}), or molar binding ratios, reflect the inherent binding proclivities of elemental cations for the various anionic moieties (such as carboxyl, sulfate, amine, hydroxyl, phosphate, and other electron-rich groups), within the nECM lattice encasing the neuron. The anionic and electron rich moieties anchor the metal to specific nodes on the lattice, serving as "addresses" for encoding the cog-info.

Table 1. Brain Levels of Elements

metal	~value	unit	+ valence
K	3.4	M	1
Na	2.7	M	1
Mg	0.3	M	2
Ca	60	mM	2
Fe	10	mM	2/3
Co	6	mM	2/3
Zn	6	mM	2
Cu	3	mM	2/1
Rb	3	mM	1
Li	~ 1	mM	1
Sc	370	uM	3
Mn	211	uM	2/3
Cr	153	uM	2/3
Al	14−20	uM	2/3
Cd	18	uM	2
Pb	3	uM	2
Hg	0.5	uM	1

The inherent bonding geometries of the elemental metals range from square planar (d^2sp^3), tetrahedral (sp^3), to octahedral (d^2sp^3), with individual bonding distances for each. Thus, each elemental oxidation state presents a unique bonding "signature". The polyanionic nECM can flex to achieve the most energetically favorable metal complexes.

The disposition of different metal cations within the nECM is modified by iontophoretic and electro-elastic effects, exerted or sensed by the neurons. The binding/desorption of hydrated metal cations to/from hydrated anionic substrates are among the most rapid biologic reactions, requiring low energy of activation (E_{act}) and generate little heat (low ΔH). The low levels of various elements (millimolar to nanomolar (10^{-3} to 10^{-9} M) concentration) further minimize heat generation.

nECM as "Information Lattice". Consider that the nECM around each neuron as a three-dimensional lattice capable of binding more than 15 different mobile components (elemental cations) as arrays/clusters/packets/stacks of almost limitless, combinatorial complexity.

The diversity of the nECM/Metal is enormous. It arises from the following:

1) Many elemental metals: various metals are present in the brain, each binding with a unique binding configuration, depending on its electron shell disposition. Some elements can exist in more than one oxidation state (i.e., $Cu^{+1/2}$, $Fe^{+2/3}$, $Mn^{+2/4/5}$).
2) The nECM is a complex lattice of polymeric components, each which present multiple anionic and electron rich moieties. These moieties can entrap metal cations; the lattice flexes to achieve the optimal disposition of groups of anionic moieties (variable size chelate rings) to accommodate the bonding preferences of the various elemental cations. Stable configurations encode cog-info.

Metal binding to a particular nECM locale (address) results in conformational changes (flexing, contraction) of the local lattice geometry, with resultant modifications in the local neural

dx.doi.org/10.1021/cn300097b | ACS Chem. Neurosci. 2012, 3, 633−642

membrane polarizabiltity/resistivity/elasticity sensed by the neuron. The [nECM/metal] complexes comprise configurable molecular switches by which neurons encode/decode cog-info.[166−195]

The computational possibilities are astronomic. The metal-binding capacity of the nECM around each neuron reflects the molar equivalents of anionic moieties, multiplied by the Avogadro number, N_A (6×10^{23}). Thus, the molar cog-info storage capacity is very large (multiples or exponentials of Avogadro's number ($N_A = 6 \times 10^{23}$). If only a fraction of the elemental cations in the nECM function in a combinatorial mode, there are enough to serve as mobile components for encoding/decoding and processing large amounts of cog-info, on which memory is based.

It is interesting to compare the operation of computer ionic memory chips with the biological mnemonic system, as in Table 2.

Table 2. Comparing Information Processing

item	computer	brain
unit component	ionic chip	neuron
matrix composition	solid state matrix	nECM hydrogel
dopant(s)	1 elemental cation	n elemental cations ($n > 10$)
construction	static hardwiring	synaptic neural network
computational format	digital	analogue
information unit	bit/word	*cuinfo*
# coding options	$n = 2$ (0,1)	$n > 10$
programming mode	$serial_2$	$parallel_n$
groupings	dedicated circuits	sparse neural ensembles
underlying physics	electro-optic/ magnetic	electro-elastic/chemical
read/write driver	voltage differential	iontophoresis, chelation
signal speed	c (speed of light)	1−80 m/s
signal frequency	50−60 Hz	2−70 kHz
energy	external (~225 W·h)	metabolism (22 W·h)

DISCUSSION

The brain contains 10^{10} to 10^{11} neurons, which can each have 10^4 excitable synapses. The histologic tissue sections by Cajal[196] and Golgi[197] (Figure 1) more than 100 years ago, which revealed neurons with synaptic contacts, were based on a selective staining process to image the neuron, but ignored the surrounding matrix. Since then, the neuron has been generally represented as a cell suspended in an "invisible" context or "space", like an interplanetary object. How can one explain the function of a ship without reference to water?

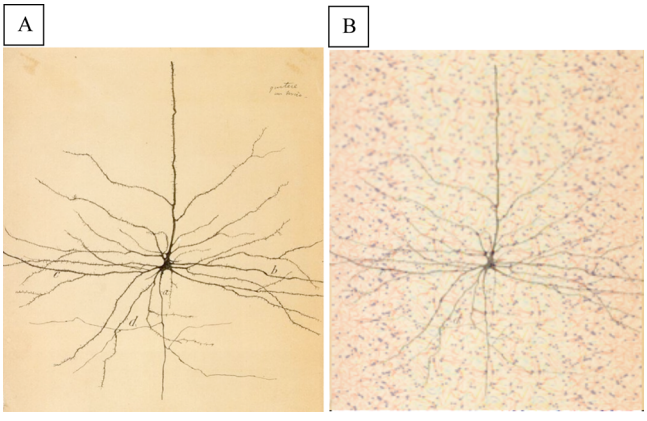


Figure 1. (A) Drawing of a single neuron by Cajal, based on Golgi's silver stain technique which ignored the nECM and (B) with superimposed image of the [nECM/metal] array, lightly stained for everything . With many histologic stains, one cannot see the neuron for the "trees" of the nECM.

Biochemists know that the "space" around the neuron is a reticulum composed of polyanionic biopolymers called the nECM.[85−135] We point out that the neuron is encased in a complex, nonhomogeneous nECM which functions both as a structural environment for the neuron, as well as a computational matrix wherein it encodes and stores cog-info.

Stacks and arrays of [nECM/metal] engulf the neuron with a continuum of stoichiometries, constituting the molecular correlates of cog-info, on which memory is based. In support of the *tripartite* mechanism of memory, we cite the following observations:

1) The literature describes effects associated with metal toxicity or deficiency, in terms of memory loss, as well as associated behavioral perturbations (confusion, disorientation, poor learning, personality changes) (Table 3).[198−209]

Table 3. Metal Correlations with Memory

metal	levels	behavioral changes
aluminum (Al)	toxic	memory loss, altered behavior, confusion, disorientation (see Alzheimer's disorder)
calcium (Ca)	deficiency	severe intellectul changes, mental retardation, poor memory
copper (Cu)	tissue overload (inherited)	Wilson's disease; psychiatric manifestations
iron (Fe)	deficiency	poor memory; dietary iron supplemetntation correlated with improvement of memory
iron (Fe)	tissue overload (inherited)	thalassemia; anxiety, depression, psychiatric disfunctions
lead (Pb)	toxic	mental deterioration, aggressive, poor memory, lower IQ
lithium (Li)	therapy (high dose)	memory improvement, mental slowness (variable reports)
magnesium (Mg)	toxic	mental confusion, impaired memory
mercury (Hg)	toxic	loss of memory, behavioral changes
thorium (Th)	toxic	mental confusion
zinc (Zn)	deficiency	loss of memory

These all indicate that perturbations of the optimum concentrations of elemental metals, either by excess or low levels, are manifest by clinically observed changes in behavioral processes, ascribed to dysfunctional memory.

2) Metabolic disorders related to metals and memory:
   - Alzheimer disorder (aluminum, zinc).
   - Wilson's disease (copper).
   - Thalassemia (iron).
   - Treatments: Li salts, zinc salts.
3) Chelation drugs that effects memory (aspirin, EDTA, deferrioxamine, penacillamine):
   - Binding of zinc by drug disrupts hippocampal-dependent spatial-working memory.
   - Chelating treatment correlated with performance tests of abstract reasoning... memory.
   - Iron chelators used to treatage-related memory dysfunction.
   - Aspirin use associated with greater prospective cognitive decline on select measures.

dx.doi.org/10.1021/cn300097b | ACS Chem. Neurosci. 2012, 3, 633−642

The ameliorative effects of chelation drugs or zinc salts suggest that optimal levels of free (diffusible) metals in the brain underlie the mechanism of memory.

4) Metallothioneins (MT; 4 isotypes) function to transport metals throughout the body, notably the brain:[210−223]
   a) Knockout mice (KO) with deletions of MT-1 and MT-2 showed poorer rates of learning, evidence of poor working memory. [223]
   b) MT dysfunction has been correlated with the following diseases or problems:
      - Autism (a disorder of neural development characterized by impaired social interaction and communication, and by restricted and repetitive behavior).
      - Behavior control and development of memory and social skills.
      - Obsessive compulsive disorders (from Web site: Herb-Discovery.com).
5) Zinc transporters (ZnT; 4 types):[225−231]
   ZnT3 KO mice have complete deficits in contextual discrimination and spatial working memory. Such animals were used to demonstrate that ZnT3 is involved in associative fear memory and extinction.
6) Tenascins C and R[114−129,133,135,232−242] are protein components of the nECM which express "fibrinogen-knobs" including haptide epitopes. KO mice, which were incapable of synthesizing tenascins, exhibited behavioral abnormalities associated with memory dysfunction.
7) Chondroitinase (an enzyme which selectively degrades chondroitins) was injected into the mouse brain, resulting in the loss of fear-driven responses. This demonstrated that learned traumatic fear memory, which usually lasts a lifetime, is located in the degradable nECM. [109]
8) Histology revealed that human brain tissue comprises significantly more nECM between neurons than chimpanzees.[101] We interpret this as indicating increased memory capacity for superior cognitive ability (e.g., language, memory).

CONCLUSION

We propose that the nECM, in combination with diffusible metal cations, is the locus wherein the neurons encode basic, molecular correlates of cog-info. The minimal cognitive unit of information (*cuinfo*) corresponds to the formation of a single metal-complex, with one or more metal cations trapped at specific chelating nodes of the nECM (presented in Figure 2).

The *cuinfo* is equivalent to the "bit" of the computer chip. Instead of representing information linearly with only two parameters (0 or 1), the neuron/[ECM/metal] complex operates with many ionic mobile components (n > 10) constrained within a flexible lattice, providing very large information storage and parallel processing capabilities.

Short-term storage of cog-info can employ trace monovalent elemental cations Li^+, Rb^+, and Cs^+ (excluding Na^+ and K^+ which are present in much higher levels to generate the intraneural high voltage potentials). The monovalent [nECM/M^{+1}] complexes are not very stable, and could be expected to decay rapidly, manifest as short-term memory (STM).

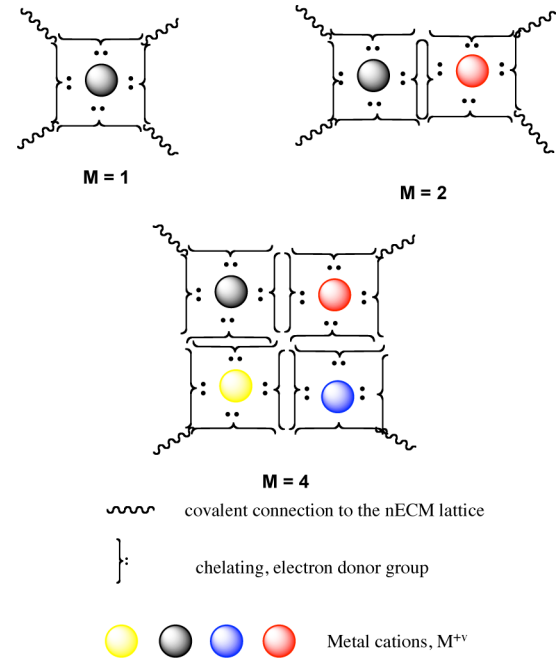


Figure 2. Schematic representation of *cuinfo** formed with M = 1, 2, or 4 metal cations per unit. Such catenary metal complex units are formed within the chelating node of the nECM, as molecular correlates of cog-info. At least one metal atom is required, though more could be involved in forming the minimal *cuinfo* ensemble.

Longer term storage of cognitive information units (derivative *cuinfo*) would employ polyvalent cations [nECM/$M^{+2/3/4/5}$] to form more stable complexes. Cross-linking, by enzymes (transglutaminases) or free radical reactions, stabilizes the *cuinfo* (metal complexes), appropriate for long-term memory (LTM).

When the [nECM/cation] arrays become degraded, the cog-info encoded therein also decays, manifesting as memory loss (storage failure). Of course, breakdowns at any critical point of the neural network chain (circuit failure) are also manifest as memory loss.

To conclude, we posit that:

- Memory is based on *tripartite* interaction of neurons, nECM, and trace elements.
- The *tripartite* mechanism involves low energetics with high speed/computational capabilities.
- Cog-info is encoded by the neuron as *cuinfo*, like bits in memory chips
- Degradation of nECM or metals excess/deficiency correlates with memory loss.
- Cited experimental observations support the proposed *tripartite* mechanism.

Just like other metabolic processes, man and animals share the biochemical basis of memory. The *tripartite* mechanism operates in all animals with brains, albeit at increasing degrees of complexity, coincident with the increasing complexity of the anatomical subunits arising from evolutionary development.

Of course, much clarification is required to discern the workings of this *tripartite* mechanism. A formalism is lacking which elaborates on how sensory input (cog-info) is encoded via the distribution of n-metals within the nECM enveloping the neurons. Detailed metabolic, viscoelastic, and dielectric characterizations of the nECM with various elemental cations would clarify the nanoscale modifications employed by neurons

dx.doi.org/10.1021/cn300097b | ACS Chem. Neurosci. 2012, 3, 633−642

to encode cog-info. Nonetheless, we identify the key physiologic compartments and suggest a credible biochemical mechanism for the phenomenon of recall.

AUTHOR INFORMATION

Corresponding Author

*E-mail: gerardmarx@gmail.com (G.M.); chaimgilon@gmail.com (C.G.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Dedicated by G.M. to his late wife, the artist Georgette Batlle, who provided a sympathetic ear and emotional support for many years. Special thanks are due to Prof. Randy Gallistel (Rutgers University) and Prof. Tamar Zelniker (Tel Aviv University) whose critical comments guided us to this condensed exposition. We would also like to thank Prof. Horst Kessler (Technical University Munchen), Prof. Sason Shaik (Hebrew University), Mr. Ron Moussafi, and our families and friends for their criticism, suggestions and support.

REFERENCES

(1) Talland, G. A., and Waugh, N. C. (1969) *The Pathology of Memory*, Academic Press, New York.

(2) Roberts, R. B., and Flexner, L. B. (1969) The biochemical basis of long-term memory. *Q. Rev. Biophys.*, 135−173.

(3) Hyden, H. (1970) The questions of a molecular basis for the memory trace. In *Biology of Memory* (Pribram, K. H., and Broadbent, D. E., Eds), Academic Press, New York, NY.

(4) Joynt, R. J. (1975) In *The Nervous System* (Tower, D. B., Ed.), Clinical Neurosciences Vol. *2*, pp 441−447, Raven Press, New York, NY.

(5) Cofer, C.N ., Ed. (1976) *Symposium on the Structure of Human Memory*, WH Freeman, New York.

(6) Kandel, E. R., and Schwartz, J. H. (1982) Molecular Biology of Memory: Modulation of Transmitter Release. *Science 218*, 433−442.

(7) Lynch, G, and Baudry, M. (1984) The biochemistry of memory: A new and specific hypothesis. *Science 224*, 1057−1063.

(8) Squire, L. R. (1986) Mechanisms of memory. *Science 232*, 1612−1619.

(9) Mishkin, M., and Appendzeller, T. (1987) The anatomy of memory. *Sci. Am. Spec. Rep. 256* (6), 80−89.

(10) Matzel, L. D., Collin, C., and Alkon, D. L. (1992) Biophysical and behavioral correlates of memory storage, degradation, and reactivation. *Behav. Neurosci. 106*, 954−963.

(11) Taubenfeld, S. M., Wiig, K. A., Bear, M. F., and Alberini, C. M. (1999) A molecular correlate of memory and amnesia in the hippocampus. *Nat. Neurosci. 2*, 309−310.

(12) McGaugh, J. L. (2000) Memory–a Century of Consolidation. *Science 287*, 248−251.

(13) Dudai, Y. (2004) The neurobiology of consolidations, or how stable is the engram? *Science 333*, 108−111.

(14) Kandel, E. R. (2006) *In Search of Memory*, Norton & Co, New York.

(15) Miller, P., and Wang, X. J. (2006) Stability of discrete memory states to stochastic fluctuations in neuronal systems. *Chaos 16*, 026109.

(16) Tsien, J. Z. (2007) Real-time neural coding of memory. *Prog. Brain. Res. 165*, 105−22.

(17) Routtenberg, A. (2008) Long-lasting memory from evanescent networks. *Eur. J. Pharmacol. 585*, 60−63.

(18) Frey, S., and Frey, J. U. (2008) 'Synaptic tagging' and 'cross-tagging' and related associative reinforcement processes of functional plasticity as the cellular basis for memory formation. *Prog. Brain Res. 169*, 117−143.

(19) Tzvetanov, T., and Womelsdorf, T. (2008) Predicting human perceptual decisions by decoding neuronal information profiles. *Biol. Cybern. 98*, 397−411.

(20) Hernandez, P. J., and Abel, T. (2008) The role of protein synthesis in memory consolidation: Progress amid decades of debate. *Neurobiol. Learn. Mem. 89*, 293−311.

(21) Gallistel, C. R., King, A. P. (2009) *Memory and the Computational Brain*, Chapter 16, Wiley Blackwell, New York.

(22) Keogh, R., and Pearson, J. (2011) Mental imagery and visual working memory. *PLoS ONE 6* (12), e29221 DOI: 10.1371/journal.pone.0029221.

(23) Ruben, M., Rojo, J., Romero-Salguero, F. J., Uppadine, L. H., and Lehn, J.,M. (2003) Grid-type metal ion architecture: Functional metallosupramolecular arrays. *Ang. Chem., Int. Ed. 43*, 3644−3662.

(24) Weitz, R. T., Walter, A., Engl, R., Sezi, R., and Dehm, C. (2006) New charge-transfer salts for reversible resistive memory switching. *Nano Lett. 6* (12), 2810−2813.

(25) Green, J. E., Choi, J. W., Boukai, A., Bunimovich, Y., Johnston-Halperin, E., DeIonno, E., Luo, Y., Sheriff, B. A., Xu, K., Shin, Y. S., Tseng, H. R., Stoddart, J. F., and Heath, J. R. (2007) A 160-kilobit molecular electronic memory patterned at 10(11) bits per square centimetre. *Nature 445*, 414−417.

(26) Gilbert, N. E., and Kozicki, M. N. (2007) An embeddable multilevel-cell solid electrolyte memory array. *IEEE J. Solid-State Circuits 42*, 1383−1391.

(27) Chen, A. (2008) Ionic memories: Status and challenges. *IEEE*, 1−5.

(28) Hutchby, J. A., Cavin, R., Zhirnov, V., Brewer, J. E., and Bourianoff, G. (2008) Emerging Nanoscale Memory and Logic Devices: A Critical Assessment. *Computer 41*, 28−32.

(29) Valov, I., Waser, R., Jameson, J. R., and Kozicki, M. N. (2011) Electrochemical metallization memories–fundamentals, applications, prospects. *Nanotechnology 22*, 254003.

(30) Lee, D. H., and Gupta, J. A. (2010) Tunable field control over the binding energy of single dopants by a charged vacancy in GaAs. *Science 330*, 1807−10.

(31) Lee, P. F., and Dai, J. Y. (2010) Memory effect of an organic based trilayer structure with Au nanocrystals in an insulating polymer matrix. *Nanotechnology 21* (29), 295706.

(32) Muralidharan, G., Bhat, N., and Santhanam, V. (2011) Scalable processes for fabricating non-volatile memory devices using self-assembled 2D arrays of gold nanoparticles as charge storage nodes. *Nanoscale 3*, 4575−4579.

(33) Lee, M. J., Lee, C. B., Lee, D., Lee, S. R., Chang, M., Hur, J. H., Kim, Y. B., Kim, C. J., Seo, D. H., Seo, S., Chung, U. I., Yoo, I. K., and Kim, K. (2011) A fast, high-endurance and scalable non-volatile memory device made from asymmetric $Ta_2O_{(5-x)}/TaO_{(2-x)}$ bilayer structures. *Nat. Mater. 10*, 625−630.

(34) Sahu, B. S., Gloux, F., Slaoui, A., Carrada, M, Muller, D., Groenen, J., Bonafos, C., and Lhostis, S. (2011) Effect of ion implantation energy for the synthesis of Ge nanocrystals in SiN films with HfO_2/SiO_2 stack tunnel dielectrics for memory application. *Nanoscale Res. Lett. 6*, 177.

(35) Stolichnov, I., Riester, S. W., Mikheev, E., Setter, N., Rushforth, A. W., Edmonds, K. W., Campion, R. P., Foxon, C. T., Gallagher, B. L., Jungwirth, T., and Trodahl, H. J. (2011) Ferroelectric polymer gates for non-volatile field effect control of ferromagnetism in (Ga, Mn)As layers. *Nanotechnology 22*, 254004.

(36) Mocatta, D., Cohen, G., Schattner, J., Millo, O., Rabani, E., and Banin, U. (2011) Heavily doped semiconductor nanocrystal quantum dots. *Science 332*, 77−81.

(37) Fernandes, M., Nobre, S. S., Rodrigues, L. C., and Gonçalves, A. Z. (2011) Li^+- and Eu^{3+}-doped poly(ε-caprolactone)/siloxane biohybrid electrolytes for electrochromic devices. *ACS Appl. Mater. Interfaces 3*, 2953−2965.

(38) Waser, R., and Aono, M. (2007) Nano-ionics-based resistive switching memories. *Nat. Mater. 6*, 833−840.

(39) Weiner, N. (1948) *Cybernetics: Or Control and Communication in the Animal and Machine*, Librairie Hermann & Cie.; MIT Press, Cambridge, MA.
(40) Shannon C. E. (1948) A mathematical theory of communication. *Bell Syst. Tech. J. 27*, 379−423; 623−656.
(41) Turing, A. (1950) Computing machinery and intelligence. *Mind 59*, 433−460.
(42) Turing, A. (1960) *Computational theory of mind*, Putnam & various publishers, New York, NY.
(43) Taub, H. A., Ed. (1963) *Design of Computers and Theory of Automata and Numerical Analysis*, John von Neumann Collected Works, Vol *V*, Pergamon Press, London.
(44) Waldrop, M. M. (1992) *Complexity: The Emerging Science at the Edge of Order and Chaos*, Viking- Penguin Press, New York.
(45) Wolfram, S. (2002) *A New Kind of Science*, Wolfram Media, Champaign, IL.
(46) Piccinini, G. (2004) The first computational theory of mind and brain: A close look at McCulloch and Pitts's "logical calculus of ideas immanent in nervous activity". *Synthese 141*, 175−215.
(47) Benenson, Y. (2009) Biocomputers: From test tubes to live cells. *Mol. BioSyst. 5*, 675−685.
(48) Spormns, O. (2011) *Networks of the Brain*, MIT Press, Cambridge, MA.
(49) Aho, A. V. (2011) What is computation? Computation and computational thinking. *Ubiquity Symposium*, Association for Computing Machinery, New York, NY.
(50) Landon, D N., and Langley, O. K. (1971) The local chemical environment of nodes of Ranvier: A study of cation binding. *J Anat. 108* (Pt 3), 419−432.
(51) Mozhaeva, G. N., and Naumov, A. P. (1973) Potassium stationary-state conductance of Ranvier's node membrane in the presence of $La^{3+,}$ Zn^{2+} and Cu^{2+} in the external medium. *Tsitologiia 15*, 1431−1435.
(52) Fox, J. M., Rojas, E., and Stämpfli, R. (1974) Blocking of sodium and potassium conductance by internal application of Zn^{2+} in the node of Ranvier. *Pflugers Arch. 351*, 271−274.
(53) Bogdanov, K. Y. (1974) [Mathematical assessment of ephaptic interaction and the recording of transmembrane potential shifts.] [Russian]. *Biull. Eksp. Biol. Med. 78* (10), 48−51.
(54) Schmitt, R. O., Dev, P., and Smith, B. H. (1976) Electronic processing of information by brain cells. *Science 193*, 114−120.
(55) Fritz, L. C., and Brockes, J. P. (1981) Clustering of ion channels at the node of Ranvier. *Nature 291*, 190−191.
(56) Kandel, E. R., and Schwartz, J. H. (1982) Molecular biology of memory: Modulation of transmitter release. *Science 218*, 433−442.
(57) Pasztor, V. M., and Bush, B. M. H. (1982) Impulse coded and analog signaling in single mechanoreceptor neurons. *Science 215*, 1635−1637.
(58) Turner, R. W., Richardson, T. L., and Miller, J. J. (1984) Ephaptic interactions contribute to paired pulse and frequency potentiation of hippocampal field potentials. *Exp. Brain Res. 54* (3), 567−70.
(59) Lynch, G., and Baudry, M. (1984) The biochemistry of memory: A new and specific hypothesis. *Science 224*, 1057−1063.
(60) Kmjevik, K. (1986) Ephaptic interactions: A significant mode of communications in the brain. *NIPS 1*, 28−29.
(61) Khulusi, S. S., Brown, M. W., and Wright, D. M. (1986) Zinc and paired-pulse potentiation in the hippocampus. *Brain Res. 363*, 152−155.
(62) Wilson, C. J., Mastronarde, D. N., McEwen, B., and Frank, J. (1992) Measurement of neuronal surface area using high-voltage electron microscope tomography. *NeuroImage 1*, 11−22.
(63) Vyvyan, H. C., Glen, J., Duncan, S., Alan, Wallén, P., and Browne, M. (1993) Measurement of total neuronal volume, surface area, and dendritic length following intracellular physiological recording. *NeuroProtocols 2*, 113−120.
(64) Jefferys, J. G. R. (1995) Nonsynaptic modulation of neuronal activity in the brain: Electric currents and extracellular ions. *Physiol. Rev. 75*, 689−723.
(65) Bokil, H., Laaris, N., Blinder, K., Ennis, M., and Keller, A. (2001) Ephaptic interactions in the mammalian olfactory system. *J. Neurosci. 21*, RC173.
(66) Debanne, D., Boudkkazi, S., Campanac, E., Cudmore, R. H., Giraud, P., Fronzaroli-Molinieres, L., Carlier, E., and Caillard, O. (2008) Paired-recordings from synaptically coupled cortical and hippocampal neurons in acute and cultured brain slices. *Nat. Protoc. 3*, 1559−1568.
(67) Roth W. T., Ford J. M., Pfefferbaum A., and Elbert T. R. (2000) Methodological issues in event-related brain potential and magnetic field studies. In *Psychopharmacology- 4th Generation* (Bloom L. E., and Kupfer D. J., Eds.), Lippincott Williams & Wilkins, Philadelphia, PA.
(68) Rasband, M. N., and Trimmer, J. S. (2001) Developmental clustering of ion channels at and near the node of Ranvier. *Dev. Biol. 236* (1), 5−16.
(69) Bear, M. F., Connors, B. W., and Pradiso, M. A. (2001) *Neuroscience: Exploring the Brain*, 2nd ed., p 97, Lippincott Williams and Wilkins, Baltimore.
(70) Lindner, B., Chacron, M. J., and Longtin, A. (2005) Integrate-and-fire neurons with threshold noise: a tractable model of how interspike interval correlations affect neuronal signal transmission. *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys. 72* (2 Pt 1), 021911.
(71) Womelsdorf, T., Schoffelen, J. M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., and Fries, P. (2007) Modulation of neuronal interactions through neuronal synchronization. *Science 316*, 1609−1612.
(72) Kampa, B. M., Letzkus, J. J., and Stuart, G. J. (2007) Dendritic mechanisms controlling spike-timing-dependent synaptic plasticity. *Trends Neurosci. 30* (9), 456−463.
(73) Tzvetanov, T., and Womelsdorf, T. (2008) Predicting human perceptual decisions by decoding neuronal information profiles. *Biol. Cybern. 98*, 397−411.
(74) Arenz, A., Silver, R. A., Schaefer, A. T., and Margrie, T. W. (2008) The contribution of single synapses to sensory representation in vivo. *Science 321*, 977−980.
(75) Cook, N. D. (2008) The neuron level phenomena underlying cognition and consciousness. *Neuroscience 153*, 556−570.
(76) Perea, G., Navarrete, M., and Araque, A. (2009) Tripartite synapses: Astrocytes process and control synaptic information. *Trends Neurosci. 32*, 421−31.
(77) Kishida, K. T., and Klann, E. (2009) Reactive oxygen species, synaptic plasticity and memory. In *Oxidative Neural Injury* (Veasey, S.C., Ed.), Chapter 1, pp 1−28, Humana Press: New York.
(78) Fries, P. (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci. 32*, 209−224.
(79) Deitmer, J. W., and Rose, C. R. (2010) Ion changes and signaling in perisynaptic glia. *Brain Res. Rev. 63*, 113−129.
(80) DeFelipe, J. (2010) From the connectotome to the synaptosome: An epic love story. *Science 330*, 1198−1201.
(81) Shelton, J. T., Elliott, E. M., Matthews, R. A., Hill, B. D., and Gouvier, W. D. (2010) The relationships of working memory, secondary memory, and general fluid intelligence: Working memory is special. *J. Exp. Psychol. 36* (3), 813−820.
(82) Lesburguères, E., Gobbo, O. L., Alaux-Cantin, S., Hambucken, A., Trifilieff, P., and Bontempi, B. (2011) Early tagging of cortical networks is required for the formation of enduring associative memory. *Science 331*, 924−928.
(83) Anastassiou, C. A., Montgomery, S. M., Barahona, M., Buzsáki, G., and Koch, C. (2010) The effect of spatially inhomogeneous extracellular electric fields on neurons. *J. Neurosci. 30*, 1925−1936.
(84) Vogels, T. P., Sprekeler, H., Zenke, F, Clopath, C, and Gerstner, W. (2011) Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science 334*, 1569−1573.
(85) Levin, E., Arieff, A., and Kleeman, C. R. (1971) Evidence of different compartments in the brain for extracellular markers. *Am. J. Physiol. 221*, 1319−1325.
(86) Nicholson, C., and Phillips, J. M. (1981) Ion diffusion modified by tortuosity and volume fraction in the extracellular microenvironment of the rat cerebellum. *J. Physiol. (Oxford, U.K.) 321*, 225−257.

(87) Hoffman, S., and Edelman, G. M. (1987) A proteoglycan with HNK-1 antigenic determinants is a neuron-associated. ligand for cytotactin. *Proc. Natl. Acad. Sci. U.S.A. 84*, 2523−2527.
(88) Iwata, M., and Carlson, S. S. (1993) A large chondroitin sulfate proteoglycan has the characteristics of a general extracellular matrix component of adult brain. *J. Neurosci. 13*, 195−207.
(89) Iwata, M., Wight, T. N., and Carlsons, S. S. (1993) A brain extracellular matrix proteoglycan forms aggregates with hyaluronan. *J. Biol. Chem. 268*, 15061−15069.
(90) Castillo, G. M., Ngo, C., Cummings, J., Wight, T. N., and Snow, A. D. (1997) Perlecan binds to the *β*-amyloid proteins (A*β*) of Alzheimer' s disease, accelerates A*β* fibril formation, and maintains A*β* fibril stability. *J. Neurochem. 69*, 2452−2465.
(91) Lander, C, Zhang, H, and Hockfield, S. (1998) Neurons produce a neuronal cell surface-associated chondroitin sulfate. *J. Neurosci. 18*, 174−183.
(92) McBain, C. J., Traynelis, S. F., and Dingledine, R. (1990) Regional variation of extracellular space in the hippocampus. *Science 249*, 674−677.
(93) Nicholson, C, and Syková, E. (1998) Extracellular space structure revealed by diffusion analysis. *Trends Neurosci. 21*, 207−215.
(94) Bukalo, O, Schachner, M, and Dityatev, A. (2001) Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. *Neuroscience 104* (2), 359−369.
(95) Yamaguchi, Y. (2000) Lecticans: Organizers of the brain extracellular matrix. *Cell. Mol. Life Sci. 57*, 276−89.
(96) Dityatev, A., and Schachner, M. (2003) Extracellular matrix molecules and synaptic plasticity. *Nat. Rev. 4*, 456−468.
(97) Kleene, R., and Schachner, M. (2004) Glycans and neural cell interactions. *Nat. Rev. Neurosci. 5*, 195−208.
(98) Syková, E. (2003) Diffusion parameters of the extracellular space. *Isr. J. Chem. 43*, 55−69.
(99) Piet, R., Vargova, L., Sykova, E., Poulain, D. A., and Oliet, S. H. R. (2004) Physiological contribution of the astrocytic environment of neurons to intersynaptic crosstalk. *Proc. Natl. Acad. Sci. U.S.A. 101*, 2151−2155.
(100) Dityatev, A., and Schachner, M. (2006) The extracellular matrix and synapses. *Cell Tissue Res. 326*, 647−654.
(101) Balter, M. (2007) News Focus: Brain evolution studies. *Science 315*, 1208−1211.
(102) Bukalo, O. (2008) Introduction: Cell adhesion and extracellular matrix molecules in synaptic plasticity. *Neuron Glia Biol. 4*, 165−167.
(103) Fischknecht, R., and Seidenbecher, C. I. (2008) The crosstalk of hyaluronan-based extracellular matrix and synapses. *Neuron Glia Biol. 4*, 249−257.
(104) Vigetti, D., Andrini, O., Clerici, M., Negrini, D., Passi, A., and Moriondo, A. (2008) Chondroitin sulfates act as extracellular gating modifiers on voltage-dependent ion channels. *Cell Physiol. Biochem. 22*, 137−146.
(105) Syková, E, and Vargová, L. (2008) Extrasynaptic transmission and the diffusion parameters of the extracellular space. *Neurochem. Int. 52* (1−2), 5−13.
(106) Bonneh-Barkay, D., and Wiley, C. A. (2009) Brain extracellular matrix in neurodegeneration. *Brain Pathol. 19*, 573−585.
(107) Hrabětov, S., Masri, D., Tao, L., Xiao, F., and Nicholson, C. J. (2009) Calcium diffusion enhanced after cleavage of negatively charged components of brain extracellular matrix by chondroitinase ABC. *Physiology 587*, 4029−4049.
(108) Kreger, S. T., and Voytik-Harbin, S. L. (2009) Hyaluronan concentration within a 3D collagen matrix modulates matrix viscoelasticity, but not fibroblast response. *Matrix Biol. 28*, 336−346.
(109) Gogolla, N., Caroni, P., Lüthi, A., and Herry, C. (2009) Perineuronal nets protect fear memories from erasure. *Science 325*, 1258−1261.
(110) Dityatev, A., Schachner, M., and Sonderegger, P. (2010) The dual role of the extracellular matrix in synaptic plasticity and homeostasis. *Nat. Rev. Neurosci. 11*, 735−746.
(111) Dityatev, A., Seidenbecher, C., and Schachner, M. (2010) Compartmentalization from the outside: The extracellular matrix and functional microdomains in the brain. *Trends .Neurosci. 33*, 503−512.
(112) Kochlamazashvili, G., Henneberger, C., Bukalo, O., Dvoretskova, E., Senkov, O., Lievens, M. J., Westenbroek, R, Engel, A. K., Catterall, W. A., Rusakov, D. A., Schachner, M., and Dityatev, A. (2010) The extracellular matrix molecule hyaluronic acid regulates hippocampal synaptic plasticity by modulating postsynaptic l-type Ca^{2+} channels. *Neuron 67*, 116−128.
(113) Bibb, J. A., Mayford, M. R., Tsien, J. Z., and Albertini, C. M. (2010) Cognition enhancement strategies. *J. Neurosci. 30*, 14987−14992.
(114) Nörenberg, U., Hubert, M., and Rathjen, F. G. (1996) Structural and functional characterization of tenascin-R (restrictin), an extracellular matrix glycoprotein of glial cells and neurons. *Int. J. Dev. Neurosci. 14*, 217−231.
(115) Milev, P., Fischer, D., Harig, M., Schulthess, T., Margolis, R. K, Chicket Ehrismann, R., and Margolis, R. U. (1997) The fibrinogen like globe of tenascin-C mediates its interactions with neurocan and phophacan/protein-tyrosine phosphatase-*β*. *J. Biol. Chem. 272*, 15501−15509.
(116) Weber, P., Rasband, M. N., Czaniera, R., Lang, Y., Bluethmann, H., Margolis, R. U., Levinson, S. R., Shrager, P., Montag, D., and Schachner, M. (1999) Mice deficient for tenascin-R display alterations of the extracellular matrix and decreased axonal conduction velocities in the CNS. *J. Neurosci. 19*, 4245−4262.
(117) Pradel, G., Schmidt, R., and Schachner, M. (2000) Involvement of L1.1 in memory consolidation after active avoidance conditioning in zebrafish. *J. Neurobiol. 43*, 389−403.
(118) Probstmeier, R., Braunewell, K., and Pesheva, P. (2000) Involvement of chondroitin sulfates on brain-derived tenascin-R in carbohydrate-dependent interactions with fibronectin and tenascin-C. *Brain Res. 863*, 42−51.
(119) Bukalo, O, Schachner, M, and Dityatev, A. (2001) Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. *Neuroscience 104* (2), 359−369.
(120) Kappler, J., Baader, S. L., Franken, S., Pesheva, P., Schilling, K., Rauch, U., and Gieselmann, V. (2002) Tenascins are associated with lipid rafts isolated from mouse brain. *Biochem. Biophys. Res. Commun. 294*, 742−747.
(121) Schumacher, S., and Stübe, E. M. (2003) Regulated binding of the fibrinogen-like domains of tenascin-R and tenascin-C to the neural EGF family member CALEB. *J. Neurochem. 87*, 1213−1223.
(122) Freitag, S., Schachner, M., and Morellini, F. (2003) Behavioral alterations in mice deficient for the extracellular matrix glycoprotein tenascin-R. Behav. *Brain Res. 145*, 189−207.
(123) Montag-Sallaz, M., and Montag, D. (2003) Severe cognitive and motor coordination deficits in tenascin-R-deficient mice. *Genes Brain Behav. 2*, 20−31.
(124) Dityatev, A, and Schachner, M. (2003) Extracellular matrix molecules and synaptic plasticity. *Nat. Rev. Neurosci. 4* (6), 456−468.
(125) Kjær, M. (2004) Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiol. Rev. 84*, 649−698.
(126) Day, J., Olin, A., Murdoch, A., Canfield, A., Sasaki, T., Timpl, R., Hardingham, T., and Aspberg, A. (2004) Alternative splicing in the aggrecan G3 domain influences binding interactions with tenascin-C and other extracellular matrix proteins. *J. Biol. Chem. 279*, 12511−12518.
(127) Lundell, A., et al. (2004) Structural basis for interactions between tenascins and lectican C-type lectin domains: Evidence for a crosslinking role for tenascins. *Structure 12*, 1495−1506.
(128) Woodworth, A., Pesheva, P., Fiete, D., and Baenziger, J. U. (2004) Neuronal-specific synthesis and glycosylation of tenascin-R. *J. Biol. Chem. 279*, 10413−10421.
(129) Syková, E., Vorísek, I., Mazel, T., Antonova, T., and Schachner, M. (2005) Reduced extracellular space in the brain of tenascin-R- and HNK-1-sulphotransferase deficient mice. *Eur. J. Neurosci. 22*, 1873−1880.

(130) Vargová, L, and Syková, E. (2008) Extracellular space diffusion and extrasynaptic transmission. *Physiol Res. 57* (Suppl 3), S89−99.
(131) Zimmermann, D. R., and Dours-Zimmermann, M. T. (2008) Extracellular matrix of the central nervous system: From neglect to challenge. *Histochem. Cell Biol. 130*, 635−653.
(132) Gurevicius, K., Kuang, F., Stoenica, L., Irintchev, A., Gureviciene, I., Dityatev, A., Schachner, M., and Tanila, H. (2009) Genetic ablation of tenascin-C expression leads to abnormal hippocampal CA1 structure and electrical activity in vivo. *Hippocampus 19*, 1232−1246.
(133) Morellini, F., Sivukhina, E., Stoenica, L., Oulianova, E., Bukalo, O., Jakovcevski, I., Dityatev, A., Irintchev, A., and Schachner, M. (2010) Improved reversal learning and working memory and enhanced reactivity to novelty in mice with enhanced GABAergic innervation in the dentate gyrus. *Cereb. Cortex 20*, 2712−2727.
(134) Dityatev, A., Schachner, M., and Sonderegger, P. (2010) The dual role of the extracellular matrix in synaptic plasticity and homeostasis. *Nat Rev Neurosci. 11* (11), 735−746.
(135) Kawakami, K., and Matsumoto, K. (2011) Behavioral alterations in mice lacking the gene for tenascin-X. *Biol. Pharm. Bull. 34* (4), 590.
(136) Henke, G., Möllmann, H., and Alfes, H. (1971) Comparative studies on the concentration of various trace elements in specific areas of the human brain using neutron activation analysis]. *Z. Neurol. 199*, 283−294 (German).
(137) Höck, A., Demmel, U., Schicha, H., Kasperek, K., and Feinendegen, L. E. (1975) Trace element concentration in human brain. Activation analysis of cobalt, iron, rubidium, selenium, zinc, chromium, silver, cesium, antimony and scandium. *Brain 98*, 49−64.
(138) Markesbery, W. R., Ehmann, W. D., Hossain, T. I., Alauddin, M., and Goodin, D. T. (1981) Instrumental neutron activation analysis of brain aluminum in Alzheimer disease and aging. *Ann. Neurol. 10*, 511−516.
(139) Tholey, G., Ledig, M., Kopp, P., Sargentini-Maier, L., Leroy, M., Grippo, A. A., and Wedler, F. C. (1988) Levels and sub-cellular distribution of physiologically important metal ions in neuronal cells cultured from chick embryo cerebral cortex. *Neurochem. Res. 13*, 1163−1167.
(140) Yinsong, W., Guisun, Z., Mingguang, T., Min, Z., and Yuandi, C. (1991) Distribution of some elements in human hair and internal organs, determined by neutron activation analysis. *J. Radioanal. Nucl. Chem. 151*, 301−311.
(141) Guisun, Z., Yinson, W., Mingguang, T., Min, Z., Yongjie, W., and Fulin, Z. (1991) Preliminary study of trace elements in human brain tumor tissues by instrumental neutron activation analysis (NAA). *J. Radioanal. Nucl. Chem. 151*, 327−335.
(142) Destasio, G., Perfetti, P., Oddo, N., Galli, P., Mercanti, D., Ciotti, M. T., Koranda, S., Hardcastle, S., Tonner, B. P., and Margaritondo, G. (1992) Metal uptake in neuron cultures: A systematic study. *NeuroReport 3*, 965−968.
(143) Yoshida, D., Ikeda, Y., and Nakazawa, S. (1993) Quantitative analysis of copper, zinc and copper/zinc ratio in selected human brain tumors. *J. Neuro-Oncol. 16*, 109−115.
(144) González, R., Guimaraes, A., Sachs, G., Rosenbaum, J., Garwood, M., and Renshaw, P. (1993) Measurement of human brain lithium in vivo by MR spectroscopy. *Am. J. Neuroradiol. 14*, 1027−1037.
(145) Plenge, P., Stensgaar, A., Jensen, H., Thomsen, C., Mellerup, E., and Henriksen, O. (1994) 24-h lithium concentration in human brain studied by Li-7 magnetic resonance spectroscopy. *Biol. Psychiatry 36*, 511−516.
(146) Sachs, G., Renshaw, P., Lafer, B., Stoll, A., Guimaraes, A., Rosenbaum, J., and Gonzalez, R. G. (1995) Variability of brain lithium levels during maintenance treatment: A magnetic resonance spectroscopy study. *Biol. Psychiatry 38*, 422−428.
(147) Al-Saleh, I., and Shinwari, N. (2001) Levels of cadmium, lead, and mercury in human brain tumors. *Biol. Trace Elem. Res. 79*, 197−203.
(148) Fitsanakis, V. A., Zhang, N., Anderson, J., Erikson, K., Avison, M., Gore, J., and Aschner, M. (2008) Measuring brain manganese and iron accumulation in rats following 14 weeks of low-dose manganese treatment using atomic absorption spectroscopy and magnetic resonance imaging. *Toxicol. Sci. 103*, 116−124.
(149) Becker, J. S., Zoriy, M. V., Pickhardt, C., Palomero-Gallagher, N., and Zilles, K. (2005) Imaging of copper, zinc, and other elements in thin section of human brain samples (hippocampus) by laser ablation inductively coupled plasma mass spectrometry. *Anal. Chem. 77*, 3208−3216.
(150) Popescu, B. F. G., Robinson, C. A., Rajput, A., Rajput, A. H., Harder, S. L., and Nichol, H. (2009) Iron, Copper, and Zinc distribution of the cerebellum. *Cerebellum 8*, 74−79.
(151) Becker, J. S. (2010) Bioimaging of metals in brain tissue from micrometre to nanometre scale by laser ablation inductively coupled plasma mass spectrometry: State of the art and perspectives. *Int. J. Mass Spectrom. 289*, 65−75.
(152) Popescu, B. F. G., and Nichol, H. (2011) Mapping brain metals to evaluate therapies for neurodegenerative disease. *CNS Neurosci. Ther. 17*, 256−268.
(153) Qin, Z., Caruso, J. A., Lai, B., Matusche, A., and Becker, J. S. (2011) Trace metal imaging with high spatial resolution: Applications in biomedicine. *Metallomics 3*, 28−37.
(154) Dwyer, F. P., and Mellor, D. P. (1964) *Chelating Agents and Metal Chelates*, Academic Press, New York.
(155) Balt, S., de Bolster, M. W., Booij, M., van Herk, A. M., and Visser-Luirink, G. (1983) Binding of metal ions to polysaccharides. V. Potentiometric, spectroscopic, and viscosimetric studies of the binding of cations to chondroitin sulfate and chondroitin in neutral and acidic aqueous media. *J. Inorg. Biochem. 19* (3), 213−26.
(156) Clark, R. W., and Bonicamp, J. M. (1998) The Ksp−Solubility Conundrum. *J. Chem. Educ. 75*, 1182−1188.
(157) Nagy, L., Yamashita, S., Yamaguchi, T., Sipos, P., Wakita, H., and Nomura, M. (1998) The local structures of Cu(II) and Zn(II) complexes of hyaluronate. *J. Inorg. Biochem. 72*, 49−55.
(158) Barbucci, R., Magnani, A., Lamponi, S., Mitola, S., Ziche, M., Morbidelli, L., and Bussolino, F. (2000) Cu(II) and Zn(II) complexes with hyaluronic acid and its sulphated derivative. Effect on the motility of vascular endothelial cells. *J. Inorg. Biochem. 81*, 229−37.
(159) Barbucci, R., Lamponi, S., Magnani, A., Piras, F. M., Rossi, A, and Weber, E. (2005) Role of the Hyal-Cu (II) complex on bovine aortic and lymphatic endothelial cells behavior on microstructured surfaces. *Biomacromolecules 6*, 212−219.
(160) Burger, K., Illés, J., Gyurcsik, B., Gazdag, M., Forrai, E., Dékány, I., and Mihályfi, K. (2001) Metal ion coordination of macromolecular bioligands: Formation of zinc(II) complex of hyaluronic acid. *Carbohydr. Res. 332*, 197−207.
(161) Donati, A., Magnani, A., Bonechi, C., Barbucci, R., and Rossi, C. (2001) Solution structure of hyaluronic acid oligomers by experimental and theoretical NMR, and molecular dynamics simulation. *Biopolymers 59*, 434−445.
(162) D'Auria, G., Flores, G., Falcigno, L., Oliva, R., Vacatello, M., Corsaro, M. M., Parrilli, M., and Paolillo, L. (2003) Hyaluronate tetrasaccharide- Cu(II) interaction: A NMR study. *Biopolymers 70*, 260−269.
(163) Barbucci, R., Lamponi, S., Magnani, A., Piras, F. M., Rossi, A., and Weber, E. (2005) Role of the Hyal-Cu (II) complex on bovine aortic and lymphatic endothelial cells behavior on microstructured surfaces. *Biomacromolecules 6*, 212−219.
(164) Tielrooij, K. J., Garcia-Araez, N., Bonn, M., and Bakker, H. J. (2010) Cooperativity in ion hydration. *Science 328*, 1006−1009.
(165) González, E., Arbiol, J., and Puntes, V. F. (2011) Carving at the nanoscale: sequential galvanic exchange and Kirkendall growth at room temperature. *Science 334*, 1377−1380.
(166) Schmitt, F. O., Dev, P., and Smith, B. H. (1997) Electronic processing of information by brain cells. *Science 193*, 114−120.
(167) Gevins, A. S., Schaffer, R. E., Doyle, J. C., Cutillo, B. A., Tannehill, R. S., and Bressler, S. L. (1983) Shadows of thought: shifting lateralization of human brain electrical patterns during brief visuo-motor task. *Science 220*, 97−99.

(168) Gevins, A. S., Doyle, J. C., Cutillo, B. A., Schaffer, R. E., Tannehill, R. S., and Bressler, S. L. (1985) Neurocognitive pattern analysis of a visuospatial task: Rapidly-shifting foci of evoked correlations between electrodes. *Psychophysiology 22*, 32−43.
(169) Gevins, A. S., Morgan, N. H., Bressler, S. L., Cutillo, B. A., White, R. M., Illes, J., Greer, D. S., Doyle, J. C., and Zeitlin, G. M. (1987) Human neuroelectric patterns predict performance accuracy. *Science 235*, 580−585.
(170) Su, M. H., Srinivasan, V., Ghanem, A. H., and Higuchi, W. I. (1994) Quantitative in vivo iontophoretic studies. *J. Pharm. Sci. 83*, 12−17.
(171) Jefferys, J. G. R. (1995) Nonsynaptic modulation of neuronal activity in the brain: Electric currents and extracellular ions. *Physiol. Rev. 75*, 689−723.
(172) Binczaka, S., Eilbeck, J. C., and Scott, A. C. (2001) Epiphaptic coupling of myelinated nerve fibers. *Physica D 148* (1−2), 159−174.
(173) Elinder, F., and Arhem, P. (2003) Metal ion effects on ion channel gating. *Q. Rev. Biophys. 36*, 373−427.
(174) Kim, S. J., Kim, H., Park, S. J., Kim, I. Y., Lee, S. H., Lee, T. S., and Kim, S. I. (2005) Behavior in electric fields of smart hydrogels with potential application as bio-inspired actuators. *Smart Mater. Struct. 14*, 511.
(175) Pietruchaa, K., and Marzecb, E. (2005) Dielectric properties of the collagen−glycosaminoglycans scaffolds in the temperature range of thermal decomposition. *Biophys. Chem. 118*, 51−56.
(176) Paradee, N., Sirivat, A., Niamlang, S., and Prissanaroon-Ouajai, W. (2012) Effects of crosslinking ratio, model drugs, and electric field strength on electrically controlled release for alginate-based hydrogel. *J. Mater. Sci. Mater. Med. 23*, 999−1010.
(177) Gelbard-Sagiv, H., Mukamel, R., Harel, M., Malach, R., and Fried, I. (2008) Internally generated reactivation of single neurons in human hippocampus during recall. *Science 322*, 96−101.
(178) Hlushkou, D., Dhopeshwarkar, R., Crooks, R. M., and Tallarek, U. (2008) The influence of membrane ion-permselectivity on electrokinetic concentration enrichment in membrane-based preconcentration units. *Lab Chip 8*, 1153−1162.
(179) Kasha, P. C., and Banga, A. K. (2008) A review of patent literature for iontophoretic delivery and devices. *Recent Pat. Drug Delivery Formulation 2*, 41−50.
(180) Grimnes, S., and Martinsen, O. M. (2008) *Bioimpedance and Bioelectricity Basics*, Academic Press, New York.
(181) Guhr, G., Schmidt, H., and Weihnacht, M. (2009) A new tool to assess mechanical and dielectric properties of tissues. *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, 729−732.
(182) Lieleg, O., Baumgärtel, R. M., and Bausch, A. R. (2009) Selective filtering of particles by the extracellular matrix: An electrostatic bandpass. *Biophys. J. 97* (6), 1569−1577.
(183) Righetti, P. G. (2009) Happy bicentennial, electrophoresis! *J. Proteomics 73*, 181−187.
(184) Miller, F. J., Weaver, K. E., and Ojemann, J. G. (2009) Direct electrophysiological measurements of hyman default network areas. *Proc. Natl. Acad. Sci. U.S.A. 106*, 12174−12177.
(185) Llinas, R. R. (1988) The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science 242*, 1654−1663.
(186) Lieleg, O., Baumgärtel, R. M., and Bausch, A. R. (2009) Selective filtering of particles by the extracellular matrix: an electrostatic bandpass. *Biophys. J. 97* (6), 1569−1577.
(187) Guiseppi-Eliea, A. (2010) Electroconductive hydrogels: Synthesis, characterization and biomedical applications. *Biomaterials 31*, 2701−2716.
(188) Paz, R., Gelbard-Sagiv, H., Mukamel, R., Harel, M., and Fried, I. (2010) A neural substrate in the human hippocampuss for linking successive events. *Proc. Natl. Acad. Sci. U.S.A. 107*, 6046−6051.
(189) Weiss S. A., Faber D. S. (2010). Field effects in the CNS play functional roles. *Front. Neural Circuits 18*, DOI: 10.3389/fncir.2010.00015.
(190) Charoo, N. A., Rahman, Z., Repka, M. A., and Murthy, S. N. (2010) Electroporation: An avenue for transdermal drug delivery. *Curr. Drug Delivery 7*, 125−36.
(191) Gratieri, T., Kalaria, D., and Kalia, Y. N. (2011) Non-invasive iontophoretic delivery of peptides and proteins across the skin. *Expert Opin. Drug Delivery 8*, 645−663.
(192) Tesselaar, E., and Sjöberg, F. (2011) Transdermal iontophoresis as an in-vivo technique for studying microvascular physiology. *Microvasc. Res. 81*, 88−96.
(193) Smirnov, A. Y., Mourokh, L. G., and Nori, F. (2011) Electrostatic models of electron-driven proton transfer across a lipid membrane. *J. Phys.: Condens. Matter 23*, 234101.
(194) Anastassiou, C. A., Perin, R., Markram, H., and Koch, C. (2011) Ephaptic coupling of cortical neurons. *Nat. Neurosci. XX*, 1−8.
(195) Alexe-Ionescu, A. L., Barbero, G., and Meyer, C. (2012) Influence of the rheological properties on the electrical impedance of hydrogels. *J. Appl. Phys. 111*, 014905.
(196) Santiago, R. C. (1906) (in German) *Studien über die Hirnrinde des Menschen v.5*, Johann Ambrosius Barth.
(197) Mazzarello, P. (2010) Golgi: A Biography of the Founder o,f Modern Neuroscience (translated by Badiani, A., and Buchtel, H. A.), Oxford University Press, New York, ISBN 970195337846.
(198) Fairhall, L. T. (1963) *Industrial Toxicology*, Hafner Publishing Co., London.
(199) Fink, E. B. (1976). In *Trace Elements in Human Health and Disease* (Prasad, A. S., and Oberlis, D., Eds.), Vol *II*, pp 1−16, Academic Press, New York.
(200) Weiss, B. (1978) The behavioral toxicology of metals. *Fed. Proc. 37*, 22−27.
(201) Johnson, F. N. (1981) The influence of alkali metal chlorides on environmentally-linked behavioral stereotypes in the rat. *Int. J. Neurosci. 13*, 199−204.
(202) Casdorph, R. H., and Walker, M. (1994) Toxic Metal Syndrome: How Metal Poisonings Can Affect Your Brain. *Dr. Morton Walker Health Book*, Penguin Putnam, New York.
(203) Chang, L. W., Ed. (1996) *Toxicology of Metals*. CRC: Boca Raton, FL.
(204) Friberg, L., Nordberg, G. F., and Vouk, V. B., Eds. (2007) *Handbook on the Toxicology of Metals*, Elsevier Publishing, New York.
(205) Kern, J. K., Grannemann, B. D., Trivedi, M. H., and Adams, J. B. (2007) Sulfhydryl-reactive metals in autism. *J. Toxicol. Environ. Health, Part A 70*, 715−721.
(206) Popke E. J. (2008) Behavioral Toxicology. In *AccessScience*, McGraw-Hill Companies, http://www.accessscience.com.
(207) Priya L., and Geetha A. (2011) Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism. *Biol. Trace Elem. Res. 142*, 148−158.
(208) Curtis, J. T., Hood, A. N., Chen, Y., Cobb, G. P., and Wallace, D. R. (2010) Chronic metals ingestion by prairie voles produces sex-specific deficits in social behavior: An animal model of autism. *Behav. Brain Res. 213*, 42−49.
(209) Murray, L., Daly, F., Little, M., and Cadgon, M. (2011) *Toxicology Handbook*, 2nd ed., Elsevier, Amsterdam.
(210) Evans, G. W., Dubois, R. S., and Hambidge, K. M. (1973) Wilson's Disease: Identification of an abnormal copper-binding protein. *Science 181*, 1175−1176.
(211) Hamer, D. H. (1986) Metallothionein. *Annu. Rev. Biochem. 55*, 913−51.
(212) Kägi, J. H. R., and Schäffer, A. (1988) Biochemistry of metallothionein. *Biochemistry 27*, 8509−8515.
(213) Nishimura, N., Nishimura, H., Ghaffar, L., and Tohyama, O. (1992) Localization of Metallothionein in the Brain of Rat and Mouse. *J. Histochem .Cytochem. 40*, 309−311.
(214) Aschner, M. (1996) The functional significance of brain metallothioneins. *FASEB J. 10*, 1129−1139.
(215) Erickson, J. C., Hollopeter, G., Thomas, S. A., Froelick, G. J., and Palmiter, R. D. (1997) Disruption of the metallothionein-III gene

in mice: Analysis of brain zinc, behavior, and neuron vulnerability to metals, aging, and seizures. *J. Neurosci. 17*, 1271−1281.
(216) Fischer, E. H., and Davie, E. W. (1998) Recent excitement regarding metallothionein Commentary. *Proc. Natl. Acad. Sci. U.S.A. 95*, 3333−3334.
(217) Palmiter, R. D. (1998) The elusive function of metallothioneins. *Proc. Natl. Acad. Sci. U.S.A. 95*, 8428−8430.
(218) Singh, V. K., and Hanson, J. (2006) Assessment of metallothionein and antibodies to metallothionein in normal and autistic children having exposure to vaccine-derived thimerosal (Hg). *Pediatr. Allergy Immunol. 17*, 291−296.
(219) Russo, A. J. (2008) Anti-Metallothionein IgG and levels of metallothionein in autistic families. *Swiss Med. Wkly. 138*, 70−77.
(220) Chung, R. S., Hidalgo, J., and West, K. A. (2008) New insight into the molecular pathways of metallothionein-mediated neuroprotection and regeneration. *J. Neurochem. 104*, 14−20.
(221) Russo, A. J. (2008) Anti-Metallothionein IgG and levels of metallothionein in autistic families. *Swiss Med. Wkly. 138*, 70−77.
(222) McAuliffe, J. J., Joseph, B., Hughes, E., Miles, L., and Vorhees, C. V. (2008) Metallothionein I,II deficient mice do not exhibit significantly worse long-term behavioral outcomes following neonatal hypoxia-ischemia: MT-I,II deficient mice have inherent behavioral impairments. *Brain Res. 1190*, 175−185.
(223) Koumura, A., Kakefuda, K., Honda, A, Ito, Y, Tsuruma, K., Shimazawa, M., Uchida, Y., Hozumi, I., Satoh, M., Inuzuka, T., and Hara, H. (2009) Metallothionein-3 deficient mice exhibit abnormalities of psychological behaviors. *Neurosci. Lett. 467*, 11−14.
(224) Levin, E. D., Perrauta, C., Pollarda, N., and Freedmanb, J. H. (2006) Metallothionein expression and neurocognitive function in mice. *Physiol. Behav. 87*, 513−518.
(225) Palmiter, R. D., Cole, T. B., Quaife, C. J., and Findley, S. D. (1996) ZnT- 3, a putative transporter of zinc into synaptic vesicles. *Proc. Natl. Acad. Sci. U.S.A. 93*, 14934−14939.
(226) Cole, T. B., Wenzel, H. J., Kafer, K. E., Schwartzkroin, P., and Palmiter, R. D. (1999) Elimination of zinc from synaptic vesicles in the intact mouse brain by disruption of the ZnT3 gene. *Proc. Natl. Acad .Sci. U.S.A. 96*, 1716−1721.
(227) Cole, T. B., Martyanova, A., and Palmiter, R. D. (2001) Removing zinc from synaptic vesicles does not impair spatial learning, memory, or sensorimotor functions in the mouse. *Brain Res. 891*, 253−265.
(228) Martel, G., Hevi, C., Friebely, O., Baybutt, T, and Shumyatsky, G. P. (2010) Zinc transporter 3 is involved in learned fear and extinction, but not in innate fear. *Learn. Mem. 17* (11), 582−590.
(229) Sindreu, C., Palmiter, R. D., and Storm, D. R. (2011) Zinc transporter ZnT-3 regulates presynaptic Erk1/2 signaling and hippocampus-dependent memory. *Proc. Natl .Acad. Sci. U.S.A. 108*, 3366−3370.
(230) Takeda, A. (2001) Significance of transferrin in iron delivery to the brain. *J. Health Sci. 47*, 520−524.
(231) Tinoco, A. D., Incarvito, C. D., and Valentine, A. M. (2007) Calorimetric, spectroscopic, and model studies provide insight into the transport of Ti(IV) by human serum transferrin. *J. Am. Chem. Soc. 129*, 3444−3454.
(232) Nörenberg, U., Hubert, M., and Rathjen, F. G. (1996) Structural and functional characterization of tenascin-R (restrictin), an extracellular matrix glycoprotein of glial cells and neurons. *Int. J. Dev. Neurosci. 14*, 217−231.
(233) Srinivasan, J., Schachner, M., and Catterall, W. A. (1998) Interaction of voltage-gated sodium channels with the extracellular matrix molecules tenascin-C and tenascin-R. *Proc. Natl. Acad. Sci. U. S. A. 95*, 15753−15757.
(234) Xiao, Z. C., Ragsdale, D. S., Malhotra, J. D., Mattei, L. N., Braun, P. E., Schachner, M., and Isom, L. L. (1999) Tenascin-R is a functional modulator of sodium channel beta subunits. *J. Biol. Chem. 274*, 26511−26517.
(235) Weber, P., Bartsch, U., Rasband, M. N., Czaniera, R., Lang, Y., Bluethmann, H., Margolis, R. U., Levinson, S. R., Shrager, P., Montag, D., and Schachner, M. (1999) Mice deficient for tenascin-R display alterations of the extracellular matrix and decreased axonal conduction velocities in the CNS. *J. Neurosci. 19*, 4245−4262.
(236) Pradel, G., Schmidt, R., and Schachner, M. (2000) Involvement of L1.1 in memory consolidation after active avoidance conditioning in zebrafish. *J. Neurobiol. 43*, 389−403.
(237) Probstmeier, R., Braunewell, K., and Pesheva, P. (2000) Involvement of chondroitin sulfates on brain-derived tenascin-R in carbohydrate-dependent interactions with fibronectin and tenascin-C. *Brain Res. 863*, 42−51.
(238) Bukalo, O, Schachner, M, and Dityatev, A. (2001) Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. *Neuroscience 104* (2), 359−369.
(239) Freitag, S., Schachner, M., and Morellini, F. (2003) Behavioral alterations in mice deficient for the extracellular matrix glycoprotein tenascin-R. Behav. *Brain Res. 145*, 189−207.
(240) Montag-Sallaz, M., and Montag, D. (2003) Severe cognitive and motor coordination deficits in tenascin-R-deficient mice. *Genes Brain Behav. 2*, 20−31.
(241) Vargová, L, and Syková, E. (2008) Extracellular space diffusion and extrasynaptic transmission. *Physiol Res. 57* (Suppl 3), S89−99.
(242) Zimmermann, D. R., and Dours-Zimmermann, M. T. (2008) Extracellular matrix of the central nervous system: From neglect to challenge. *Histochem. Cell Biol. 130*, 635−653.

NOTE ADDED AFTER ISSUE PUBLICATION

This paper was published on the web on August 15, 2012, with the August 2012 issue. The blank reference 189 has been deleted (and subsequent references renumbered) in this online version published August 31, 2012, and an Addition and Correction appears on the Web on August 31, 2012, and in the September 2012 issue.