ACS Chemical Neuroscience

Research Article

pubs.acs.org/chemneuro

The Molecular Basis of Memory. Part 2: Chemistry of the *Tripartite* Mechanism

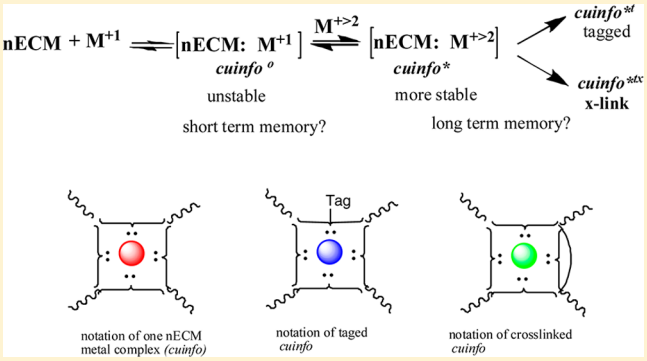
Gerard Marx*

MX Biotech Ltd., Jerusalem, Israel

Chaim Gilon*

Institute of Chemistry, Hebrew University, Jerusalem, Israel

ABSTRACT: We propose a *tripartite* mechanism to describe the processing of cognitive information (cog-info), comprising the (1) neuron, (2) surrounding neural extracellular matrix (nECM), and (3) numerous "trace" metals distributed therein. The neuron is encased in a polyanionic nECM lattice doped with metals (>10), wherein it processes (computes) and stores cog-info. Each [nECM:metal] complex is the molecular correlate of a cognitive unit of information (*cuinfo*), similar to a computer "bit". These are induced/sensed by the neuron via surface iontophoretic and electroelastic (piezoelectric) sensors. The generic *cuinfo* are used by neurons to biochemically encode and store cog-info in a rapid, energy efficient, but computationally expansive manner. Here, we describe chemical reactions involved in various processes that underline the *tripartite* mechanism. In addition, we present novel iconographic representations of various types of *cuinfo* resulting from"tagging" and cross-linking reactions, essential for the indexing *cuinfo* for organized retrieval and storage of memory.



KEYWORDS: *Memory, tripartite model, cognitive unit of information (cuinfo), neuron, extracellular matrix, trace metal*

What is biologic memory? How can one describe the sensation of "memory" in molecular terms? What is the atomic correlate of memory? How is memory stored and lost? What formalism describes the encoding and storage of cognitive information (cog-info)?

One would like to formulate a molecular mechanism that is physiologically credible and biochemically based. It must operate rapidly (faster than neural firing at <100 ms) with available biological materials in an aqueous environment at 37 °C, using ~400 cal/day, and offer huge computational capabilities. It should permit a chemical explanatory framework for describing "synaptic plasticity" and "long-term potentiation" (LTP)[1−6] or forgetting.

In a previous article, we proposed a "*tripartite*" mechanism, wherein neurons, encased in a lattice of neural extracellular matrix (nECM), employ more than 10 trace metals (dopants) to encode, store, and decode cog-info.[7] The neurons employ the nECM as an "information lattice", comparable to the workings of a computer memory chip which encodes, stores, and retrieves binary "bits" (0/1) in an inorganic matrix. Neurons also release vesicles containing neurometals (Cu^{2+}, Zn^{2+}). We cited the literature which correlates the appropriate availability of trace elements as well as the functioning of nECM, with recall or memory. Due to limitations of space, we will not repeat the arguments and the cited references in our previous article.[7] Rather, below we summarize and expand on the underlying chemistry[8−27] and neuroelectric biology[28−38] of the *tripartite* mechanism, as it relates to the nECM with trace metals.[39−46]

Definitions. The following terms are defined here for later discussions, as follows:

- *Tripartite* System: Memory emerges from the dynamic interaction of three physiologic compartments:
  1. Neurons
  2. Neural extracellular matrix (nECM), encasing the neuron
  3. Trace metals, dispersed within the nECM (dopants)
- cog-info: Abbreviation of "cognitive information" referring to basic unit of information obtained from the senses, employed by the neuron to compute (mentate).
- *cuinfo:* Cognitive unit of information, embodied as a [nECM:metal] complex (singular and plural); the molecular correlate of cog-info, equivalent to computer bit, which is used by the neuron as an information packet.

Received: January 28, 2013
Accepted: February 18, 2013
Published: February 18, 2013

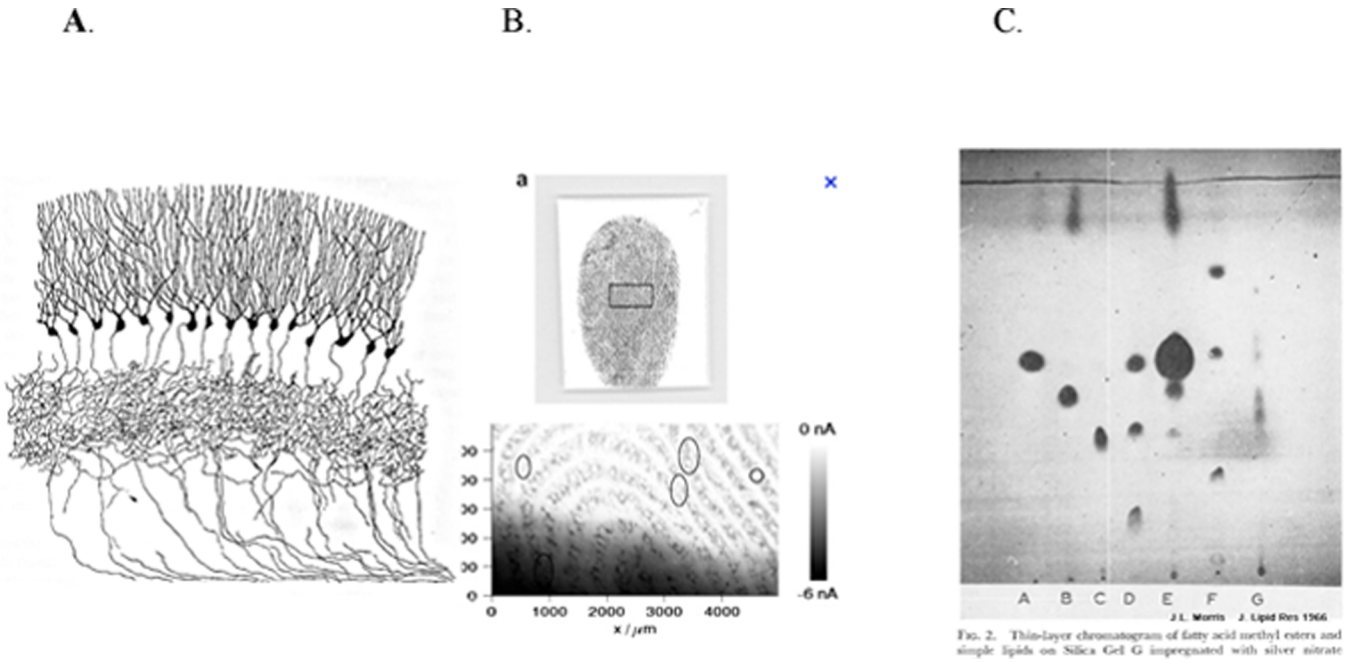


Figure 1. Silver stain of (A) hippocampus neurons by Golgi (note the blank background). Reprinted from ref 98. (B) Forensic fingerprint (no cells). Reprinted with permission from ref 49. Copyright 2007 ASBMB. (C) Thin layer chromatogram of lipids. Reprinted with permission from ref 47. Copyright 1966 Elsevier.

The computational components of the brain, the neuron and neural circuits, operate by electric and chemical signaling in an aqueous, but not empty, extracellular environment, comprising nECM with dispersed trace metal "dopants".

Neuron. The neuron is intimately connected to the external nECM by numerous electrically active surface features, notably, integrins, gap junctions, nodes of Ranvier, and chemical and electrical synapses. These are sensitive to the nanoscale dielectric, piezoelectric, and elastic properties of the nECM. Some proteins (tenascin) can attach directly to the neural membrane, providing another channel for neural interdigitation with the nECM. Thus, the neuron can be described as a cell that is intimately connected to its environment by virtue of the many electroeffectors, sensors, and receptors on its surface membrane.

Comments on the Histology of Neurons. The structure of the neuron was initially elucidated from the histological works of Golgi and Cajal and many subsequent neurobiologists. They used a silver nitrate staining method, wherein atomic silver is deposited as nanoparticles, outlining cell structures.

$$\underset{\substack{\text{hydrophobic double bonds}\\ \text{soluble, clear}}}{Ag^{+1}} \xrightarrow{\text{redox}} \underset{\substack{\text{insoluble silver}\\ \text{(Tollen's test)}}}{Ag^{0}} \xrightarrow{O_2} \underset{\substack{\text{insoluble black}\\ \text{(Golgi, Cajal)}}}{Ag_2O}$$

Analytic chemists know that soluble silver salts (i.e., $AgNO_3$) in aqueous solutions are clear and uncolored. Experimental observations indicate that the cation Ag^+ attaches particularly to lipids (especially double bonds (C═C).[47,48] Exposure to a reducing agent generates elemental silver (Ag^0), detected as a shiny surface precipitate (e.g., the Tollen's test for reducing sugars). Shiny silver is easily oxidized, becoming visibly black (Ag_2O). Thus, Golgi and Cajal used the Ag^+ nitrate stain to selectively visualize the lipidic neural surface membranes as well as intraneural compartments (nucleus, vesicles) of the newly identified neurons with synaptic connectors (Figure 1A). The silver stain technique has been also used to identify lipids for forensic[49] (Figure 1B), chromatographic applications[47] (Figure 1C) and neurotoxicity testing.[50]

As the nECM is mainly a three-dimensional (3D) mesh composed of polysaccharide with very few reducing sugars, it does not react with the Ag^+. Subsequent histologists with other types of stains (Nissle, immunochemical) continued this tradition of exclusively imaging the neuron as the main player in brain function, ignoring the contribution of the nECM. The converse of the tale of the "Emperor's New Clothes" comes to mind. Everyone, save one boy, perceived the Emperor as clothed, though he was naked. Here, the neuron is viewed as naked, in synaptic contact with other, similarly naked, neurons, though the neurons are "clothed" with nECM.

nECM Characterization. The nECM can be described as a block copolymer, comprising a number of glycosaminoglycans (GAGs), polysaccharides of varying dimensions, as well as various proteins (for more details, see the appropriate references in ref 7).[51−56] All these contribute many electron rich (Lewis base) moieties that cooperatively chelate individual metal cations. These anionic coordination groupings are termed "binding pocket", "chelating node", or "address". The binding characteristics of each metal cation for the electron rich (i.e., amine, carboxyl, phosphate, sulfate, hydroxyl, ether) moieties of the nECM is reflected by quantitative chemical parameters such as

K_D = dissociation constant

K_{sp} = solubility constant

CEC = critical electrolyte constant

These parameters reflect the inherent affinity of metals (found in the brain) with the electron rich, moieties presented by the nECM. The entrapment of a metal cation "locked" at a specific configuration/shape, effectively is defined herein as *cuinfo* (see below), sensed by the neuron.

Metals. The elemental metals are each uniquely distributed among the brain's anatomic compartments. While most of the metals are present within the neurons, a significant amount, about 10%, is present in the nECM. Table 1 summarizes the gross levels of a number of elements in the brain, arranged as sets of monovalent, divalent, and polyvalent elements.

Table 1. Groups of Brain Elements

metal	level	conc. unit
	monovalent	
K^+	3.4	M
Na^+	2.7	M
Rb^+	3	mM
Li^+	~1	mM
Cs^+	~1	mM
	divalent	
Mg^{+2}	0.3	M
Ca^{+2}	60	mM
Zn^{+2}	6	mM
	polyvalent: redox active	
$Al^{+2/3}$	14−20	uM
$Co^{+1/2}$	6	mM
$Cu^{+1/2}$	3	mM
$Cr^{+2/3}$	153	uM
$Fe^{+2/3}$	40	mM
$Mn^{+2/3}$	211	uM

Their distribution is not homogeneous, differing among anatomic compartments. Today's invasive techniques, such as neutron activation analysis, atomic spectroscopy, mass spectrometry, and fluorescent labeling,[57] only permit such analysis on ex vivo slices of the brain.

The process by which neurons specifically accumulate and store each of the elements is not generally known. Vesicles containing Ca^{2+} are known to be released upon neural activation (firing). Little else has been described regarding the selectivity of neurons for one or another traces elemental cation or their accumulation of redox activators (ascorbate, glutathione). However, it is apparent that the trace metals and some oxidants within the blood permeate the nECM to reach the neurons via passage through the nECM surrounding the cell.[52−56] Some metals may freely diffuse through the nECM; others may be actively transported by metallothioneins or other metal transporters.

RESULTS AND DISCUSSION

Metal Binding Configurations. The elemental metal cations (Figure 2A) dispersed within the nECM each can achieve a number of bonding geometries consonant with their electron shell disposition. For example, a divalent metal complex wherein the central atom is combined with 6 different electron rich moieties could exist in 15 geometrically isomeric forms (Figure 2B). Most metal cations diffuse through the nECM as hydrated cations, combined with at lease 4 water molecules each.

In aqueous environments, monovalent elemental cations (Li^+, Na^+, K^+, Rb^+, Cs^+) are not capable of forming strong chelate bonds. They usually exist as tetrahedral water complexes, with coordination radii in the range 2.2−3.3 Å (0.2−0.3 nm). Chelate complexes with monovalent elements in water are not very stable and tend to disintegrate. Notwithstanding, these metals are present in the brain at millimolar levels with diffusion coefficients D ranging from 13 × 10^{-6} to 21 × 10^{-6} cm^2/s. Thus, they are available to rapidly form short-lived complexes, possibly correlated to short-term memory (STM).

By contrast, divalent and polyvalent elemental cations can form a multitude of more stable chelate complexes, consonant with each element's electron shell organization.[8−19,58] For example, Ca^{2+} is tetra coordinate with a diffusion coefficient (in nECM) on the order of 2−3 × 10^{-6} cm^2/s. Zn^{2+}, which has a complex electron shell, is not redox active but can achieve a few bonding geometries, most frequently tetrahedral as well as square pyramidal and octahedral configurations (see Figure 2B). Similar descriptions can be made for all the di- and trivalent metal cations, each which can attach to selected coordination sites within the nECM, each achieving unique binding configurations. Assuming a chelation bond with two

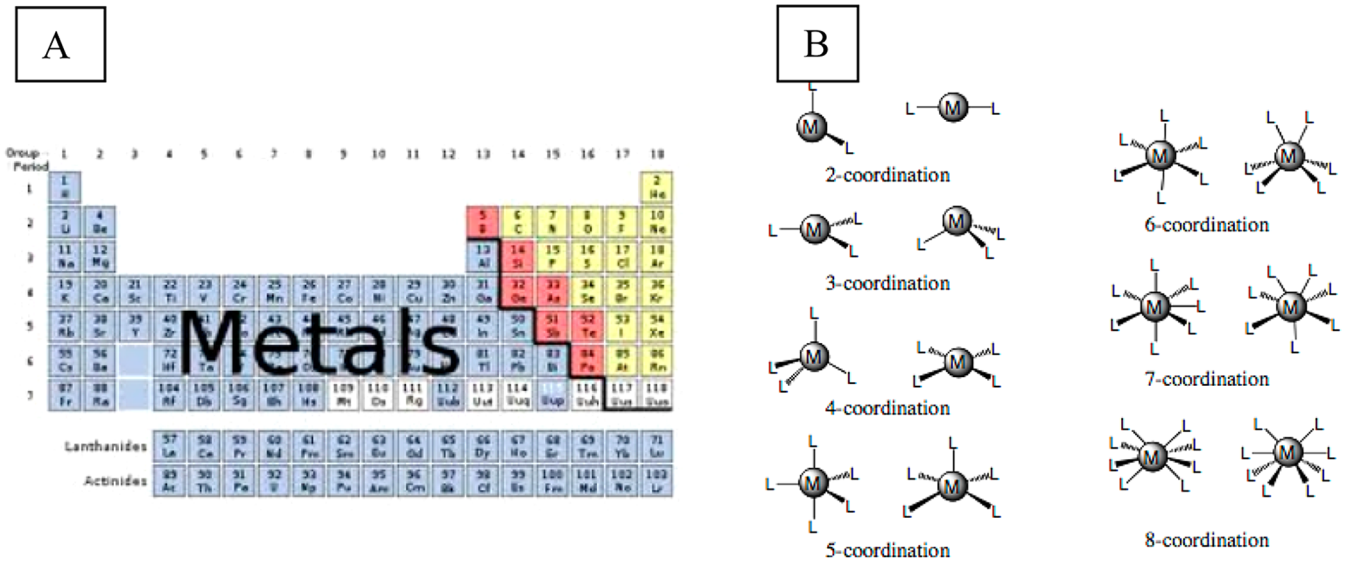


Figure 2. (A) Table of elements, emphasizing the physiologically relevant trace metals. (B) Configurational possibilities of a single metal cation binding to multiple anionic moieties (chelating node).

dx.doi.org/10.1021/cn300237r | ACS Chem. Neurosci. 2013, 4, 983−993

anionic sites, one could formulate the metal complexation reactions as (Figure 3):

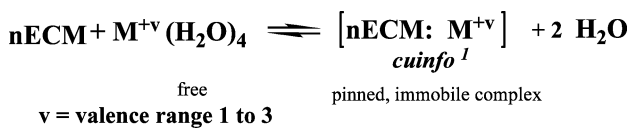


Figure 3. Reaction of hydrated metal cation with nECM.

The nECM is a highly hydrated gel with many associated water molecules attached thereto. The water allows electrical current to dissipate through the nECM and also serves to hydrate the M^{+v}, discarded as leaving groups upon chelation. Common usage generally ignores the solvent when describing chemical reactions; so shall we.

The term "mechanism" is employed here, in a chemical manner. It describes a chemical reaction at molecular- or atomic-scale stages, where atomic elements interact with one another to make or break covalent or ionic chemical bonds, forming molecules and molecular complexes.

In that spirit, we propose that the formation of [nECM:metal] complexes with monovalent and polyvalent elemental cations represents the minimal cognitive unit of information (*cuinfo*). The initially formed, but unstable, monovalent complexes become transformed into polyvalent complexes, which are generally more stable, as follows (Figure 4):

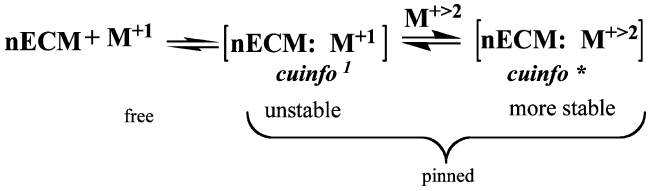
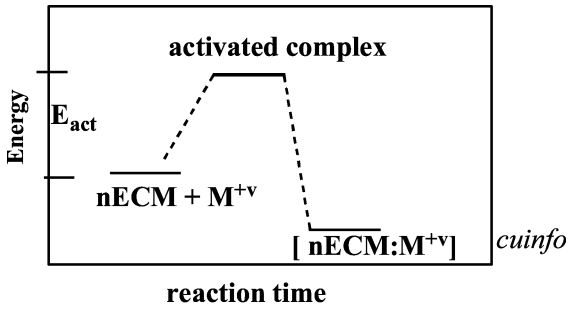


Figure 4. Scheme of the reaction of monovalent and divalent metal cation with nECM.

The energetic of metal complexation to the nECM to form *cuinfo*, is outlined in the energy diagram below (Figure 5):



$$\text{Rate} = A^* e^{-(E_{act} / k_B T)}$$

Figure 5. Free energy diagram for complexation of M^{+v} to nECM, the kinetics of which are described by the Boltzmann rate equation. The energy of activation (E_{act}) is low, the rate is rapid (k_B = Boltzmann constant), and the reaction is not very exothermic (v = valency state, usually from 0 to +3).

The illustration is meant to point out that the free energy (ΔG), enthalpy (ΔH), as well as the activation energy (E_{act}) for adsorption/desorption of metal cations to polyanionic substrates to form *cuinfos* are all low, characterized by rapid rates with little heat generation.

The energetic of metal complexation reactions (on the order of 5−10 kcal/mol) permit rapid, but not always reversible, dynamics. At physiologic levels (concentration of 10^{-6}−10^{-9} M), the trace elements in the nECM bind with low energy requirements (5−10 kcal/mol, the brain expending 400 cal/day), generating little heat, but affording huge combinatorial coding options. By contrast, the Blue Gene IBM supercomputer operates at 100 petaflops/s and uses more that 6.6 MW/h.

Redox Reactions. Multivalent elements, such as copper, iron, and manganese, can achieve more than 2 oxidation states, each with a number of complexation geometries, as summarized in Table 2.

Table 2. Coordinating Configurations

oxid state	val config	coord no.	shape
Cu^{+1}	d^{10}	4	tetrahedral
Cu^{+2}	d^{9}	4	square planar
		5	trigonal-bipyramid
		5	square-pyramidal
		6	octahedral
Zn^{+2}	d^{10}	4	tetrahedral
		5	square-pyramidal
		6	octahedral
Fe^{+2}	d^{6}	4	tetrahedral
		5	trigonal bipyramid
		6	octahedral
Fe^{+3}	d^{5}	4	tetrahedral
		6	octahedral
		7	pentagon-bipyramid

Small redox activators, notably oxygen, ascorbate (0.7 mM in nECM), and glutathione (1 mM),[59−63] with diffusion coefficients of 2−4, 1.6, and 5.6×10^{-6} cm^2/s, respectively, are also present in the nECM.[64−66] Thus, the significant concentrations of redox ingredients for site-specific Fenton reactions with reactive metals are present in the neuron and the nECM. A Fenton reaction occur with cationic copper cycles between oxidation states of Cu(I) and Cu(II). Similarly, iron cycles between Fe(II) and Fe(III) (see Figure 6).

Tagging Metal Complex via Redox Reactions. As a consequence of local redox reactions between oxidants (such as ascorbate and glutathione) and multivalent metal complexes, carbonyl groups could be formed on the many glycans comprising the nECM. The many sugars and proteins that make up the nECM are rich in oxidation prone groups (such as primary and secondary hydroxyl OH) that could be oxidized into carbonyl (C═O) groups. Thus, the OH radicals, locally generated by the Fenton reaction, can derivatize the nECM lattice, by introducing aldehyde or keto carbonyl groups at specific locations, or causing carbohydrate ring-opening, leading to the formation of flexible "hinges" (Figure 7). Thus, $[nECM:M^{+2/3}]$ complex, designated as *cuinfo**, could be tagged with one or more unique carbonyl moieties, with concomitant unique nanostructural, viscoelastic, and dielectric alterations,

dx.doi.org/10.1021/cn300237r | ACS Chem. Neurosci. 2013, 4, 983−993

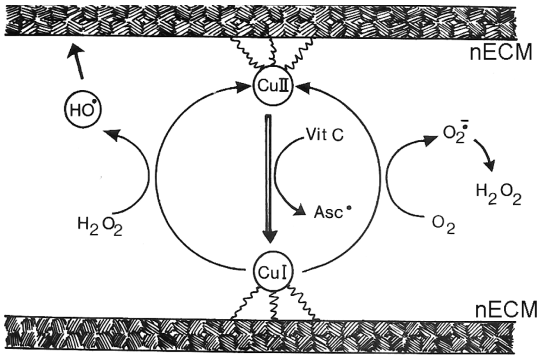


Figure 6. Schematic representation of the site-specific Fenton reaction based on the interaction of nECM-bound $Cu^{+1/2}$ with ascorbate, to generate reactive OH radicals, generating new keto C═O from C−OH groups.

referred to as *cuinfo**[t]. This process would provide the cog-info complex with an identifier, a "tag" for sorting and easier recall, such as required to remember strong stimuli (pain, fear, hunger, pleasure, attention). Also, the tagged *cuinfo**[t] could help index (classify) the stored cog-info, accelerating recall.

There are multiple positions available in the saccharide subunits of the nECM (chondroitins, heparans, hyaluronates) for such carbonyl formation. Each saccharide (sugar) ring usually presents more than three oxidizable hydroxyl (OH) groups.

Ascorbate and glutathione are redox drivers of such reactions. For example, ascorbate is a very reactive molecule. In blood,[59−63] it is sequestered within platelets, with high internal platelet ascorbate levels (mM range), compared to low blood plasma levels (μM range). An ascorbate level in neurons has been determined to be in the 1−10 mM range.[55−57] Thus, the neuron has the resources (polyvalent metals and oxidants) to affect redox Fenton reactions within the nECM, whenever it is appropriately activated.

Stabilizing Metal Complexes within the nECM. *a. Enzymatic Cross-linking.* An additional mechanism that forms and affects long-term memory is cross-linking reactions affected by enzymes in the nECM, such as transglutaminases,[12] which induce the formation of a covalent amide linkage between amine and primary amide moieties (such as Lys and Gln side chains), as follows (Figure 8):

The resultant amide bond is not susceptible to peptidases. For example, a fibrin clot is rendered more stable by the cross-linking induced by factor XIII (a transglutaminase). Cross-linking renders the [nECM:metal] complex (a *cuinfo*) more stable, suitable for long-term storage, but available for recall.

Nonenzymatic Cross-Linking via Free Radical (Fenton) Reactions. As a consequence of local redox reactions between oxidants (such as ascorbate and glutathione) and multivalent metal complexes, carbonyl groups (keto or aldehyde) could be formed on the many carbohydrates comprising the nECM (see above). The carbonyl groups can spontaneously condense with amine ($-NH_2$) groups forming imines (Schiff bases) as follows (Figure 9):

The Schiff base reaction is reversible. It can be maintained by the hydrophobic conditions, such as found in hydrophobic pocket of proteins, which greatly increases its stability. Conversely, exposure to hydrating conditions with slight pH variations could reverse the direction of the reaction, breaking the immine linkage.

Thus, the redox reaction leading to aldo/keto group formation, could effectively derivatize the [nECM:metal] complex, and also lead to cross-linking reactions, stabilizing the ensemble, ensuring storage of encoded cog-info.

Other condensation reactions between carbonyl groups, giving rise to cross-links, are shown in Figure 10. Aldol condensation[12] can occur in physiological media either by enzymatic catalysis (aldolases) or occur spontaneously by general base catalysis. The aldol condensation causes the formation of a covalent C−C bond. Such reactions have been

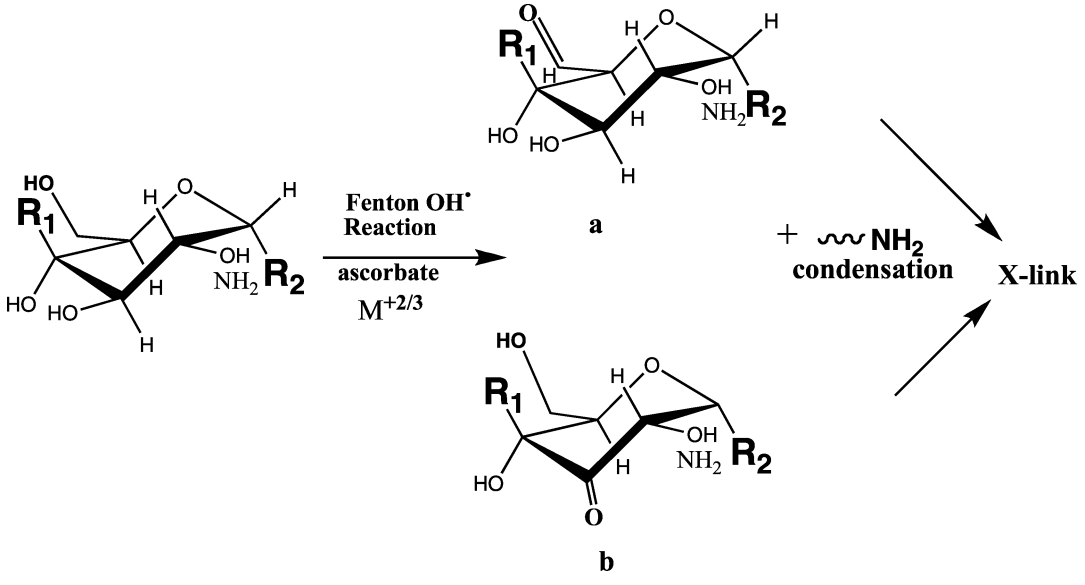


Figure 7. Monomeric saccharide unit (glucose or glucosamine for example), within the nECM polymeric matrix (sites R and R_2), showing multiple hydroxyl groups, capable of being oxidized to carbonyl groups by the Fenton reaction: aldehyde (a above) or keto group (only one isomer shown in b). A neighboring amino group from other glycans (e.g., amino sugars) or imbedded proteins can engage in condensation reactions causing cross-linking (see below).

dx.doi.org/10.1021/cn300237r | ACS Chem. Neurosci. 2013, 4, 983−993

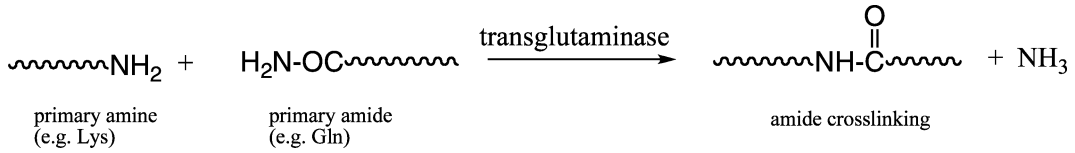


Figure 8. General reaction scheme of cross-linking by transamidation.

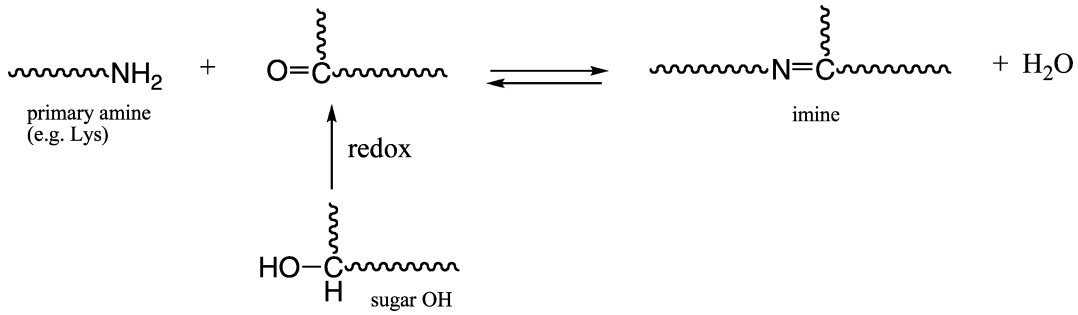


Figure 9. General reaction scheme of Schiff base cross-linking reaction.

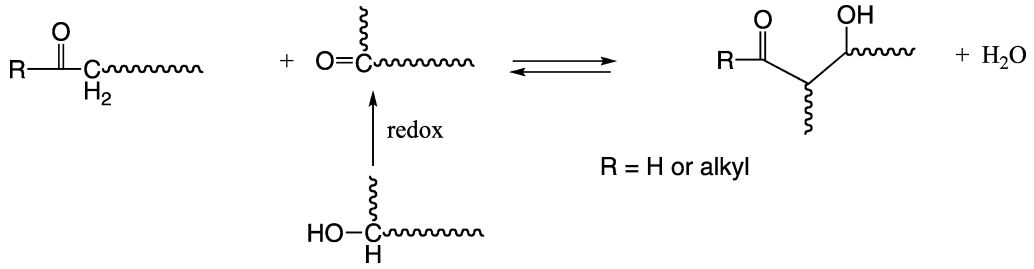


Figure 10. General reaction scheme of aldol condensation after oxidation of hydroxyl group.

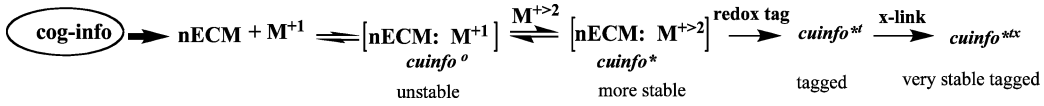


Figure 11. Reaction scheme for hierarchical formation of various types of *cuinfo*.

shown to occur in the eye and the extracellular matrix of other tissues.

Other types of cross-links can be formed, such as those induced by lysyl oxidase-dependent and those originating from stochastic processes, such as the Maillard reaction, oxidation (for instance, dityrosine), and lipid peroxidation (such as malonyl dialdehyde-lysine cross-links).[67−71]

The essential point here is that a number of cross-linking reactions and locales are available for stabilizing the [nECM:metal] complexes, effectively ensuring long-term storage of *cuinfo* encoding cog-info, critical to memory. Alternatively, these processes can occur in an uncontrolled manner in pathological states in which memory is destroyed (e.g., dementia and Alzheimer's disease).

Generations of *cuinfo*. The scheme whereby various generations of *cuinfo* are transformed by various reactions described above is outlined in Figure 11.

Iconographic representation of various classes of *cuinfo* is shown in Figure 12.

Pathways involving transglutaminase enzymes, or redox reactions (involving Schiff base condensation, etc), further stabilize the complex by introducing one or more cross-linkers, rendering the metal complex more enduring.

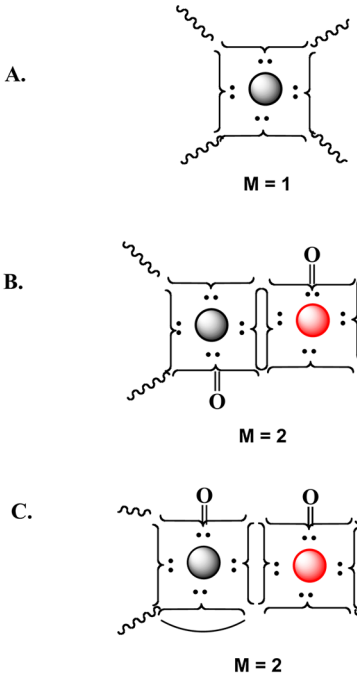
Tagging *cuinfo*. Aside from the above-discussed Fenton reaction, other modes of tagging *cuinfo** could involve reactions such as acetylation, phosphorylation,[72] sulfation, and methylation. These types of reactions are known to turn on/off certain metabolic pathways for proteins, DNA, and carbohydrates and are used in signal transductions.

Combinatorial Diversity of Tagging and Cross-Linking. We have described five types of tags (C═O, OAc, SO_3^-, PO_3^-, OMe) and three types of cross-links (tranglutaminates, Schiff base, and aldol condensates) (Figure 13). For every *cuinfo* complex, the nECM provides many potential moieties for affecting these reactions. Thus, in addition to the multitude of metal cations (n > 10) to form the *cuinfo** complex, the Avogadro-scale combinatorial options[17−19] for tagging and cross-linking each *cuinfo** are also staggeringly huge (iconographic representation, Figure 13).

Hypothetical Model of *cuinfo* Formed with Tenascin and Zn^{2+}. Tenascins[73,74] are scattered throughout the nECM as monomers, trimers, or hexamers (star shapes).[75−78] Knockout mice deficient in tensacins exhibited defective memory.[79−82]

The fibrinogen globe terminating the tenascins contains polypeptides that are homologous to the C-termini of the β and γ chains of fibrinogen. This region (D-domain) in fibrinogen

dx.doi.org/10.1021/cn300237r | ACS Chem. Neurosci. 2013, 4, 983−993



[nECM:Metal] complexes with 1 or 2 metal atoms corresponding to:
A. *cuinfo* (generic)
B. *cuinfo* ^{*t} (tagged)
C. *cuinfo* ^{*tx} (gtagged and cross-linked)

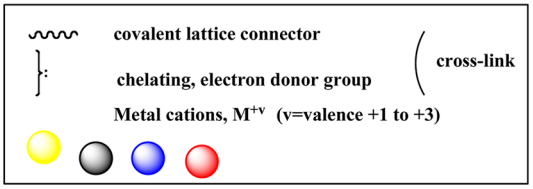
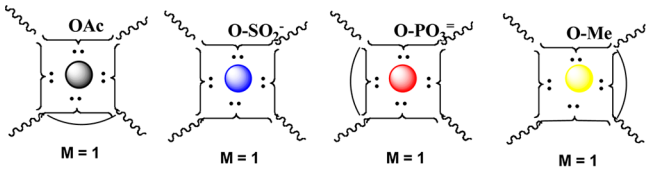


Figure 12. Iconographic icons of various types of *cuinfo* (singular/plural). (A) Metal complexes, the correlates of *cuinfo**, formed with 1 or 2 metals per unit. (B) Tagged *cuinfo**^{t}, modified to express a keto (C═O) carbonyl, resulting from a Fenton-reaction generating ^{OH}radicals (tagged). (C) Cross-linked *cuinfo**^{tx}.

has been shown to bind Zn^{2+} with an affinity on the order of K_D 18 uM, affecting coagulation parameters, such as clotting time, clot turbidity, ultrastructure, and viscoelasticity.[83−92] Also, the C-terminal epitope (Haptide) has been shown to be capable of attaching directly to and penetrating the lipid bilayer membrane of mesenchymal cells,[93−97] as well as neurons (Marx unpublished).

Thus, we propose a hypothetical scheme whereby the tenascins attach directly to the neuron via their Haptide termini. The binding of Zn^{2+} alters the conformation/position of the epitope, effectively encoding cog-info as a *cuinfo**, affected/sensed by the neurons with iontophoretic/piezo-electric actuators embedded within the membrane (Figure 14).

The above Figure 14 presents a hypothesized scheme whereby Zn^{2+} binding to a fibrinogen-like region of tenascin induces a local conformational change in the protein, sensed at the neural surface as a "*cuinfo* event". Other cations could also be entrapped by the nECM to form variant *cuinfo**. Consonant with each element's unique bonding traits (chelating bond lengths and angles), each type of cation binding event would impose its unique imprint (signal) on the conformation/



[nECM:Metal] complexes corresponding to tagged and cross-linked *cuinfo* ^{*t} and *cuinfo* $^{*t\,x}$ respectively.

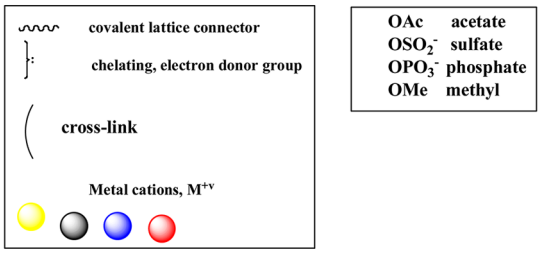


Figure 13. Iconographic representations of tagged and/or cross-linked *cuinfo**^{t} and *cuinfo**^{tx}, respectively, with different elemental cations, tagged with acetyl (Ac), sulfate (SO_3^-), phosphate (PO_3^-), or methyl (OMe) moieties. Such derivatized *cuinfo* serve to index the encoded cog-info for organized storage required for easier recall.

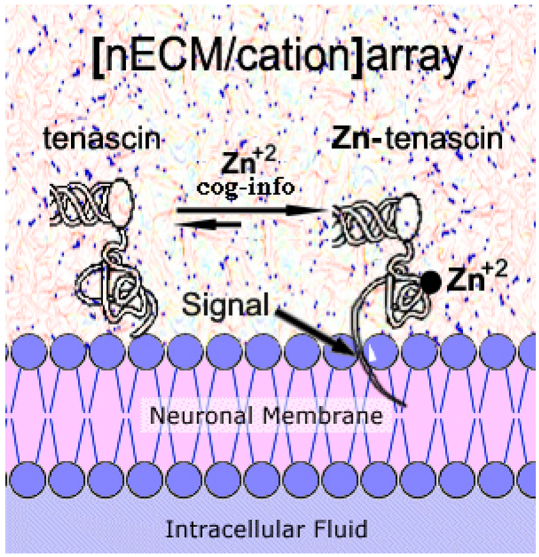


Figure 14. Hypothesized encoding event of tenascin (a component of the nECM) in direct contact with the neuronal membrane. Upon binding, a Zn^{2+} atom, a conformational/positional change in the Haptide epitope perturbs the membrane, serving as an encoding event, to form the *cuinfo**.

position of the haptide epitope, induced or sensed by the neuron.

How can one describe a physiologically credible system wherein cog-info is transformed into memory? The proposed mechanism must conform to the limiting conditions of chemistry and physiology, in terms of low energy and rapid kinetics, but provide large encoding capacity. It should be couched in terms reflecting the biochemical underpinnings of all physiologic processes.

Golgi and Cajal developed the silver staining method, whose underlying chemistry we review here. Neurobiologists generally overlooked the nECM, imaging neurons "a la Cajal", as if they were naked, suspended in space. Ironically, Cajal's neural images with blank backgrounds blinded subsequent generations of neurobiologists to the importance of the nECM for neural

dx.doi.org/10.1021/cn300237r | ACS Chem. Neurosci. 2013, 4, 983−993

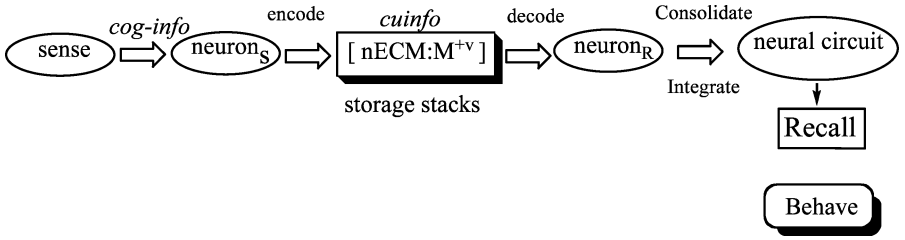


Figure 15. Conceptualized process whereby cog-info is encoded as [nECM:metal] complexes (*cuinfo*) and decoded by the neuron and neural circuitry, resulting in recall (memory), driving behavior.

function. By contrast, the *tripartite* mechanism focuses on the nECM as a key component in neural processing of cog-info (mentation), ultimately sensed as recall.

Neurons are remarkably like blood platelets. Both accumulate metabolites, cofactors, and reactants in cytoplasmic granules or vesicles, which are released upon activation. For example, platelets accumulate ascorbate, zinc, fibrinogen, coagulation factors, and so forth in various granules or special cytoplasmic compartments which are released upon activation, all aiding the formation of a stable blood clot. The neurons also accumulate NTs, ascorbate, and trace metals within vesicles, released by action potentials. But to what purpose? We suggest that the neurons manipulate or sense the surrounding ensembles of [nECM:metal] complexes (*cuinfo*), using piezoelectric, viscoelastic, and iontophoretic sensors/actuators to encode and decode cognitive information (cog-info), from which the neural circuit integrates and consolidates memory. The nECM around the neuron is a relatively static lattice, but the trace metals distributed therein are mobile (dopants), whose reversible binding or desorption from a particular address are sensed by the neuron.

However, such sensing is not binary ($n = 2$), but multinary ($n > 10$). We respectfully defer more detailed discussion of the computational aspects of the *tripartite* mechanism to a subsequent manuscript (MBM Pt4).

Each bound element imposes a unique geometry to the adsorption locale (address), which is reflected by conformational twisting/dielectric modification, sensed by the neuron. However, metal binding reactions are inherently reversible, with a lifetime depending on the particular element and the anionic moieties. For example, monovalent cations form relatively short-lived complexes, compared to di- and trivalent elemental metals.

Cross-linking imposes covalent constraints on the [nECM:-metal] complexes (*cuinfo*), rendering them much more stable, as exemplified by the cross-linking of fibrin by factor XIII. Transglutaminase enzymes impose covalent cross-links, rendering the *cuinfo*^{x} much more resistant to degradative enzymes, effectively permanent. Some cross-linking reactions (Schiff base, aldol condensation, Maillard reaction) are themselves reversible, with stability dictated by local pH and/or enzymes. Cross-linking (i.e., stabilizing) the *cuinfo*^{x} is iconographically represented by the "bow" notation in the Figure 12.

We conceive a process whereby the input of sensorial cog-info is encoded within the nECM by metal "dopants". The initially formed, but unstable, monovalent metal complex (template *cuinfo*^{1}), is transposed and transformed into ever more stable sets of polyvalent metal complexes (*derivative cuinfo*) by various types of chemical transformations. We described Fenton reactions (redox) (Figure 6), condensation reactions between oxidized saccharide units (Figures 8, 9, and 12), as well as cross-linking by enzymatic pathways. Some of these occur in the ECM of various types of tissue, notably bone, skin, and eyes. Detailed evaluation of such reactions in brain tissue awaits further elaboration.

A hypothetical overview of the process of sensing an external event as cog-info involves its transformation into a storable form in the brain but outside the neuron (as *cuinfo*), available for recall by the neural circuitry. The *tripartite* mechanism permits one to chemically describe a sequence of processes, to rationalize the encoding and recall of cog-info as memory (Figure 15). It addresses the issue of how cog-info can be stored for long periods for recall (short- and long-term memory), and forgotten (by degradation or lack of critical components).

■ CONCLUSIONS

The chemical structures and processes described above are the basis for a molecular description of memory. It explains the highly efficient almost unlimited computational power of the human brain, using minimal amount of energy (400 cal/day equivalent to energy consumption of a standard laptop computer) with minimal heat generation, in aqueous media. The chemical interactions of the *tripartite* mechanism underlie "long term potentiation (LTP)" or synaptic plasticity, manifest as short- and long-term memory. Hopefully, the above discussion will stimulate efforts to characterize molecular correlates of declarative, episodic, procedural, and other types of memory.

■ AUTHOR INFORMATION

Corresponding Author

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

Author Contributions

Both authors have equal contribution.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated by G.M. to his late wife, the artist Georgette Batlle, for hearth, heart, and art. We thank our friends and family for their encouragement. Special thanks are due to Prof. Randy Gallistel (Rutgers University) and Prof. Tamar Zelniker (Tel Aviv University), whose critical comments guided our composition of these serialized expositions. We have no conflict of interest but are looking for academic and commercial collaborators.

REFERENCES

(1) Hopfield, J. J. (1982) Neural networks and physical systems with emergent selective computational abilities. *Proc. Natl. Acad. Sci. U.S.A. 79*, 2554−2558.

(2) Compte, A., Brunel, N., Goldman-Rakic, P. S., and Wang, X. J. (2000) Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. *Cereb. Cortex 10*, 910−923.

(3) Craver, C. F. (2003) The making of a memory mechanism. *J. Hist. Biol. 36*, 153−195.

(4) Amit, D. J. (2013) Hebb versus biochemistry: The fundamental viewpoint. In *Dan Amit memorial volume*. In print.

(5) Mongillo, G., Barak, O., and Tsodyks, M. (2008) Synaptic theory of working memory. *Science 319*, 1543−1546.

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

(7) Marx, G., and Gilon, C. (2012) The molecular basis of memory. *ACS Chem. Neurosci. 3*, 633−642.

(8) Pauling, L. (1960) *The Nature of the Chemical Bond*, 3rd ed, Cornell University Press, Ithaca, NY.

(9) Angeleci, R. J. (1973) Stability of coordination compounds. In *Inorganic Biochemistry*, Vol *1*, Chapter 2, Elsevier Scientific Publishers, Amsterdam.

(10) Greenwood, N. N., and Earnshaw, A. (1997) *Chemistry of the Elements*, 2nd ed., Butterworth-Heinemann, Oxford, UK.

(11) Berg, J. M., Tymoczko, J. L., and Stryer, L. (2002) *Textbook of Biochemistry*, Freeman & Company, New York.

(12) Lehninger, A., Nelson, D. L., and Cox, M. M. (2009) *Principles of Biochemistry*, Freeman & Company, New York.

(13) Dwyer, F. P., and Mellor, D. P. (1964) *Chelating Agents and Metal Chelates*, Academic Press, New York.

(14) Martell, A., and Smith, P. M.(1977) *Critical Stability Constants*, Vols. *1*−*4*, Plenum Press, New York.

(15) Kettle, S. F. A. (1971) *Coordination Compounds*, Thomas Nelson & Sons, Edinburgh, UK.

(16) Clark, R. W., and Bonicamp, J. M. (1998) The Ksp−Solubility Conundrum. *J. Chem. Educ. 75*, 1182−1188.

(17) Tielrooij, K. J., Garcia-Araez, N., Bonn, M., and Bakker, H. J. (2010) Cooperativity in ion hydration. *Science 328*, 1006−1009.

(18) Knobloch, B., Mucha, A., Operschall, B. P., Sigel, H., Jeżowska-Bojczuk, M., Kozłowski, H., and Sigel, R. K. O. (2011) Stability and Structure of Mixed-Ligand Metal Ion Complexes That Contain Ni2+, Cu2+, or Zn2+, and Histamine, as well as Adenosine 5′-Triphosphate (ATP4) or Uridine 5′-Triphosphate (UTP4): An intricate network of equilibria. *Chem.—Eur. J. 17*, 5393−5403.

(19) Solov'ev, V., Marcou, G., Tsivadze, A., and Varnek, A. (2012) Complexation of Mn^{2+}, Fe^{2+}, Y^{3+}, La^{3+}, Pb^{2+}, and UO_2^{2+} with organic ligands: QSPR Ensemble Modeling of Stability Constants. *Ind. Eng. Chem. Res. 51*, 13482−13489.

(20) Van Harreveld, A., Dafny, N., and Khattab, F. I. (1971) Effects of calcium on the electrical resistance and the extracellular space of cerebral cortex. *Exp. Neurol. 31*, 358−367.

(21) 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*, 213−226.

(22) Olsher, U., Izatt, R. M., Bradshaw, J. S., and Kent, N. (1991) Coordination chemistry of lithium ion: A crystal and molecular structure review. *Chem. Rev. 91*, 137−164.

(23) Guo, X., Zhu, G., Fang, Q., Xue, M., Tian, G., Sun, J., Li, X., and Qiu, S. (2005) Synthesis, structure and luminescent properties of rare earth coordination polymers constructed from paddle-wheel building blocks. *Inorg. Chem. 44*, 3850−3855.

(24) Meighan, S. E., Meighan, P. C., Choudhury, P., Davis, C. J., Olson, M. L., Zornes, P. A., Wright, J. W., and Harding, J. W. (2006) Effects of extracellular matrix-degrading proteases matrix metalloproteinases 3 and 9 on spatial learning and synaptic plasticity. *J. Neurochem. 96*, 1227−1241.

(25) Vorisek, I., and Sykova, E. (2009) Measuring diffusion parameters in the brain: comparing the real-time iontophoretic method and diffusion-weighted magnetic resonance. *Acta Physiol. 195*, 101−110.

(26) Bates, F. S., Hillmyer, M. A., Lodge, T. P., Bates, C. M., Delaney, K. T., and Fredrickson, G. H. (2012) Multiblock polymers: Panacea or pandora's box? *Science 336*, 434−440.

(27) Geddes, L. A., and Baker, L. E. (1967) The specific resistance of biological material—a compendium of data for the biomedical engineer and physiologist. *Med. Biol. Eng. 5*, 271−293.

(28) Trubatch, J., and Van Harreveld, A. (1972) Spread of iontophoretically injected ions in a tissue. *J. Theor. Biol. 36*, 355−66.

(29) Llinas, R. R. (1988) The intrinsic electrophysiological properties of mammalian neurons: Insights into central nervous system function. *Science 242*, 1654−1665.

(30) Bear, M. F., Connors, B. W. and Pradiso, M. A. (2001) *Neuroscience: Exploring the Brain*, 2nd ed., p 97, Lippincott Williams and Wilkins, Baltimore.

(31) Jefferys, J. G. R. (1995) Nonsynaptic modulation of neuronal activity in the brain: Electric currents and extracellular ions. *Physiol. Rev. 75*, 689−723.

(32) Bokil, H., Laaris, N., Blinder, K., Ennis, M., and Keller, A. (2001) Ephaptic interactions in the mammalian olfactory system. *J. Neurosci. 21*, RC173.

(33) Hrabìtová, S., and Nicholson, C. (2007) Biophysical properties of brain extracellular space explored with ion-selective microelectrodes, integrative optical imaging and related techniques. In *Electrochemical Methods for Neuroscience* (Michael, A. C., and Borland, L. M., Eds.), Chapter 10, CRC Press, Boca Raton, FL.

(34) Deitmer, J. W., and Rose, C. R. (2010) Ion changes and signaling in perisynaptic glia. *Brain Res. Rev. 63*, 113−129.

(35) Tich, J., Erhart, J., Kittinger, E., Privratska, J., and Privatska, J. (2010) *Fundamentals of Piezoelectric Sensorics: Mechanical, Dielectric, and Thermodynamical Properties of Piezoelectric Materials/Edition 1*, Springer-Verlag, New York.

(36) Tamano, H., and Takeda, A. (2011) Dynamic action of neurometals at the synapse. *Metallomics 3*, 656−661.

(37) Gianni, C., and Menciassi, A. (Eds.) (2012) *Piezoelectric nanomaterials for biomedical applications*, Nanomedicine and Nanotoxicology Series, Springer-Verlag, New York.

(38) Liu, Y., Zhang, Y., Chow, M. J., Chen, Q. N., and Li, j. (2012) Biological ferro-electricity uncovered in aortic walls by piezoresponse force microscopy. *Phys. Rev. Lett. 108*, 078103.

(39) Frederickson, R. E., Frederickson, C. J., and Danscher, G. (1990) In situ binding of bouton zinc reversibly disrupts performance on a spatial memory task. *Behav. Brain Res. 39*, 25−33.

(40) Takeda, A. (2000) Movement of zinc and its functional significance in the brain. *Brain Res. Rev. 34*, 137−148.

(41) Frederickson, C. J., Won Suh, S., Silva, D., Frederickson, C. J., and Thompson, R. B. (2000) Importance of zinc in the central nervous system: The zinc-containing neuron. *J. Nutr. Suppl.*, 1471S−1483S.

(42) Mathie, A., Sutton, G. L., Clarke, C. E., and Veale, E. L. (2006) Zinc and copper: Pharmacological probes and endogenous modulators of neuronal excitability. *Pharmacol. Ther. 111*, 567−583.

(43) Madsen, E., and Gitlin, J. D. (2007) Copper and iron disorders of the brain. *Annu. Rev. Neurosci. 30*, 317−337.

(44) Paoletti, P., Pergnano, A. M., Barbour, B., and Casado, M. (2009) Zinc at glutamatergic synapses. *Neuroscience 158*, 126−136.

(45) Lutsenko, S., Bhattacharjee, A., and Hubbard, A. L. (2010) Copper handling machinery of the brain. *Metallomics 2*, 596−608.

(46) Tamano, H., and Takeda, A. (2011) Dynamic action of neurometals at the synapse. *Metallomics 3*, 656−661.

(47) Morris, L. J. (1966) Separation of lipids by silver ion (Ag^+) chromatography. *J. Lipid Res. 7*, 717−732.

(48) Bothun, G. D. (2008) Hydrophobic silver nanoparticles trapped in lipid bilayers: Size distribution, bilayer phase behavior, and optical properties. *J. Nanobiotechnol. 6*, 13−20.

(49) Zhang, M., and Girault, H. H. (2007) Fingerprint imaging by scanning electrochemical microscopy (and silver stain). *Electrochem. Commun. 9*, 1778−1782.
(50) Switzer, R. C. (2000) Application of silver degeneration stains for neurotoxicity testing. *Toxicol. Pathol. 28*, 70−83.
(51) Maroudas, A., Weinberg, P. D., Parker, K. H., and Winlove, C.P . (1988) The distributions and diffusivities of small ions in chondroitin sulphate, hyaluronate and some proteoglycan solutions. *Biophys. Chem. 32*, 257−270.
(52) Scott, J. E. (1995) Extracellular matrix, supramolecular organisation and shape. *J. Anat. 187* (Pt 2), 259−269.
(53) Hrabetová, S., Masri, D., Tao, L., Xiao, F., and Nicholson, C. (2009) Calcium diffusion enhanced after cleavage of negatively charged components of brain extracellular matrix by chondroitinase ABC. *J. Physiol. 587* (Pt16), 4029−4049.
(54) Vargova, L., Homola, A., Cicanic, M., Kuncova, K., Krsek, P., Marusic, P., Sykova, E., and Zamecnik, J. (2011) The diffusion parameters of the extracellular space are altered in focal cortical dysplasias. *Neurosci. Lett. 499*, 19−23.
(55) Androjna, C., Gatica, J. E., Belovich, J. M., and Derwin, K. A. (2008) Oxygen diffusion through natural extracellular matrices: Implications for estimating ″critical thickness″ values in tendon tissue engineering. *Tissue Eng,. Part A. 14*, 559−569.
(56) Bath, B. D., White, H. S., and Scott, E. R. (2000) Electrically facilitated molecular transport. Analysis of the relative contributions of diffusion, migration, and electro-osmosis to solute transport in an ion-exchange membrane. *Anal. Chem. 72*, 433−42.
(57) Taki, M., Iyoshi, S., Ojida, A., Hamachi, H., and Yamamoto, Y. (2010) Development of highly sensitive fluorescent probes for detection of intracellular copper(i) in living systems. *J. Am. Chem. Soc. 132*, 5938−5939.
(58) Fabbrizzi, L., and Poggi, A. (2012) Anion recognition by coordinative interactions: Metal−amine complexes as receptors. *Chem. Soc. Rev. 42*, 1681−1699.
(59) McCulloch, R. K., and Vandongen, R. (1992) Measurement of ascorbic acid in platelets and its relationship to polymorphonuclear leukocyte levels. *Clin. Chim. Acta 213*, 15−22.
(60) Seghieri, G., Martinoli, L., di Felice, M., Anichini, R., Fazzini, A., Ciuti, M., Miceli, M., Gaspa, L., and Franconi, F. (1998) Plasma and platelet ascorbate pools and lipid peroxidation in insulin-dependent diabetes mellitus. *Eur. J. Clin. Invest. 28*, 659−63.
(61) Sahud, M. A., and Aggeler, P. M. (1970) Utilization of ascorbic acid during platelet aggregation. *Proc. Soc. Exp. Biol. Med. 134*, 13−18.
(62) Lloyd, J. V., Davis, P. S., Emery, H., and Lander, H. (1972) Platelet ascorbic acid levels in normal subjects and in disease. *J. Clin. Pathol. 25*, 478−483.
(63) Kitagawa, S., Fujisawa, H., Kametani, F., and Sakurai, H. (1992) Generation of active oxygen species in blood platelets: Spin trapping analysis. *Free Radical Res. Commun. 15*, 319−324.
(64) Rice, M. E. (1999) Ascorbate compartmentalization in the CNS. *Neurotox. Res. 1*, 81−90.
(65) Qiu, S., Li, L., Weeber, E. J., and May, J. M. (2007) Ascorbate transport by primary cultured neurons and its role in neuronal function and protection against excitotoxicity. *J. Neurosci. Res. 85*, 1046−1056.
(66) May, J. M. (2012) Vitamin C transport and its role in the central nervous system. *Subcell. Biochem. 56*, 85−103.
(67) Nagaraj, R. H., Shipanova, I .N., and Faust, F. M. (1996) Protein cross-linking by the Maillard reaction. Isolation, characterization, and in vivo detection of a lysine-lysine cross-link derived from methylglyoxal. *J. Biol. Chem. 271*, 19338−19345.
(68) Monnier, V. M., Mustata, G. T., Biemel, K. L., Reihl, O., Lederer, M. O., Zhenyu, D., and Sell, D. R. (2005) Cross-linking of the extracellular matrix by the Maillard reaction in aging and diabetes: an update on ″a puzzle nearing resolution″. *Ann. N.Y. Acad. Sci. 1043*, 533−544.
(69) Sell, D. R., Biemel, K. M., Reihl, O., Lederer, M. O., Strauch, C. M., and Monnier, V .M. (2005) Glucosepane is a major protein cross-link of the senescent human extracellular matrix. Relationship with diabetes. *J. Biol. Chem. 280*, 12310−12315.
(70) Kishida, K. T., Klann, E. (2009) Reactive oxygen species, synaptic plasticity and memory. In *Oxidative Neural Injury* (Veasey, S. C., Ed.), Ch 1, pp 1−28. Humana Press, New York.
(71) Fan, X., Sell, D. R., Zhang, J., Nemet, I., Theves, M., Lu, J., Strauch, C., Halushka, M. K., and Monnier, V. M. (2010) Anaerobic *vs* aerobic pathways of carbonyl and oxidant stress in human lens and skin during aging and in diabetes: A comparative analysis. *Free Radical Biol. Med. 49*, 847−856.
(72) Yalak, G., and Vogel, V. (2012) Extracellular phosphorylation and phosphorylated proteins: Not just curiosities but physiologically important. *Sci. Signaling 5* (255), re7.
(73) Erickson, H. P. (1994) Evolution of the tenascin family-implications for function of the C-terminal fibrinogen-like domain. *Perspect. Dev. Neurobiol. 2*, 9−19.
(74) Lafleur, D. W., Chiang, J., Fagin, J. A., Schwartz, S. M., Shah, P. K., Wallner, K., Forrester, J. S., and Sharifi, B. G. (1997) Aortic smooth muscle cells interact with tenascin-C through its fibrinogen-like domain. *J. Biol. Chem. 272*, 32798−32803.
(75) 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*, 15753−15777.
(76) 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.
(77) Schenk, S., Chiquet-Ehrismann, R., and Battegy, E. J. (1999) The fibrinogen-globe of tenascin-C promotes basic-FGF-induced endothelial cell elongation. *Mol. Biol. Cell 10*, 2933−2943.
(78) Scheetz, M., Jones, F., and Jones, P. L. (2000) The Tenascin family of ECM glycoproteins: Structure, function, and regulation during embryonic development and tissue remodeling. *Dev. Dyn. 218*, 235−259.
(79) Brenneke, F., Bukalo, O., Dityatev, A., and Lie, A. A. (2004) Mice deficient for the extracellular matrix glycoprotein tenascin-r show physiological and structural hallmarks of increased hippocampal excitability, but no increased susceptibility to seizures in the pilocarpine model of epilepsy. *Neuroscience 124*, 841−855.
(80) 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.
(81) 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.
(82) Kawakami, K., and Matsumoto, K. (2011) Behavioral alterations in mice lacking the gene for tenascin-X. *Biol. Pharm. Bull. 34*, 590.
(83) Marx, G., Gurfel, D., and Hopmeier, P. (1987) Zinc alters fibrin ultrastructure. *Thromb. Haemostasis 57*, 73−76.
(84) Marx, G. (1987) Protofibrin coagulation induced by calcium or zinc. *Biopolymers 26*, 911−920.
(85) Marx, G. (1988) Elasticity of fibrin and protofibrin gels is differentially modulated by calcium and zinc. *Thromb. Haemostasis 59*, 500−503.
(86) Marx, G. (1988) Modelling cation-driven (proto)fibrin coagulation. *Biopolymers 29*, 1233−1241.
(87) Marx, G. (1988) Divalent cation induce protofibril gelation. *Am. J. Hematol. 27*, 104−109.
(88) Marx, G. (1988) Mechanism of fibrin coagulation based on selective, cation-driven protofibril association. *Biopolymers 27*, 763−774.
(89) Marx, G. (1988) Zinc binding to fibrinogen and fibrin. *Arch. Biochem. Biophys 266*, 285−288.
(90) Hopmeier, P., Halbmayer, M., Fischer, M., and Marx, G. (1990) Zinc modulates thrombin adsorption to fibrin. *Thrombos. Res. 58*, 293−302.

(91) Marx, G., Krugliak, J., and Shaklai, M. (1991) Nutritional zinc increases platelet sensitivity to agonists. *Am. J. Hematol. 38*, 161−165.
(92) Marx, G., Korner, G., Mou, X., and Gorodetsky, R. (1993) Packaging zinc, fibrinogen and factor XIII in platelet α-granules. *J. Cell. Physiol. 156*, 437−442.
(93) Gorodetsky, R., Vexler, A., An, J., Mou, X., and Marx, G. (1998) Haptotactic and growth stimulatory effects of fibrin(ogen) and thrombin on cultured fibroblasts. *J. Lab. Clin. Med. 131*, 269−280.
(94) Gorodetsky, R., Vexler, A., Shamir, M., An, J., Levdansky, L., Shimeliovich, I., and Marx, G. (2003) New cell attachment peptide sequences from conserved epitopes in the carboxy termini of fibrinogen. *Exp. Cell Res. 287*, 116−129.
(95) Gorodetsky, R., Levdansky, L., Vexler, A., Shimeliovich, I., Kassis, I., Ben-Moshe, M., Magdassi, S., and Marx, G. (2004) Liposome transduction into cells enhanced by haptotactic peptides (Haptides) homologous to fibrinogen C-termini. *J. Controlled Release 95*, 477−488.
(96) Marx, G., Ben-Moshe, M., Magdassi, S., and Gorodetsky, R. (2004) Fibrinogen C-terminal peptidic sequences (Haptides) modulate fibrin polymerization. *Thromb. Haemostasis 91*, 43−51.
(97) Marx, G., and Gorodetsky, G. (2009) Haptotactic peptides. U.S. Patent #7,544,655.
(98) Golgi, C. (1906) Nobel Lecture: The Neuron Doctrine − Theory and Facts. *The Nobel Prize in Physiology or Medicine 1906*, Nobel Foundation.