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The Molecular Basis of Neural Memory Part 11: Chem-electric Write /Read Processes

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ABSTRACT

What constitutes the code whereby the brain stores and recalls emotive memory? We suggest that neural recall is based on the “tripartite” interactions of three physiologic compartments:

- **Neurons** - networked, sparse ensembles.
- **Neural Extracellular Matrix (nECM)** - A hydrogel with a polysaccharide lattice surrounding neurons.
- **Dopants** (metals and neurotransmitters (NTs)) - ejected from vesicles. The nECM performs as a “memory material” wherein a neuron imprints incoming cognitive information as a c dopant code comprising trace metals and NTs (which elicit physiologic as well as emotive effects).

To “write”, the neuron ejects vesicles containing dopants into the surrounding nECM, a process analogous to ink-jet printing on paper. A pattern of metal-centered complexes is “written” within the nECM around the neurons, effectively encoding cognitive unit(s) of information (*cuinfo*).

To “read”, the neuron employs at least 3 types of “sensors”, aggregates of proteins (i.e., mosaics embedded within its membrane, examples being GPCR mosaics, K2P channels and acetylcholine receptors (AcCholR)), all of which number many thousands per neuron. They perform as dynamic chemo-sensors (reported diffusion: 10^{-1} to 10^{-3} um²/sec), which transform the *cuinfo* code, the “engrams” around individual neurons, into chemo-electric synaptic signals.

The neural net transforms and consolidates the chemical signals into coherent psychic states, also instigating reactions of glands and muscles.

Keywords: Cognitive information, Emotions, Neurotransmitter, Trace metal, Psycho-chemistry

BACKGROUND

“It was as if I discovered a whole new universe of chemical elements and had begun to see certain relations between them, but had no means to organize the whole series into a harmonious and coherent union.”

-Thomas Wolfe: The Story of a Novel (1936)

“The past is beautiful because one never realises an emotion at the time. It expands later and thus we do not have complete emotions about the present, only about the past.”

-Virginia Woolf (1882-1904)

Man may control what he thinks (sometimes), but not how. How does the brain in animals and man, composed entirely of matter, experience the psychic talent of persistent recall, to guide behavior?

One could say:

“Mind and memory are inseparable aspects of the mentating brain.” Leaving aside spirits, ghosts, quantum entanglements and ethereal entities (literature too vast to cite here), one queries: What happens between “sensation” and “action”, that we recall as “memory”?

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"All mental processes are biological. Therefore, any disorder must also have a biological basis".

-Kandel [1]

To the above quote, one could easily substitute the word "chemical" for "biological". We modern neuroscientists desire a unifying principle for memory, but do not want explanations based on ghosts, spirits, black holes, strings or quantum uncertainty.

Just as today's medical diagnoses and clinical treatments are based on chemical considerations, we turn to the discipline of chemistry for mechanistic clarification of a mental state, such as memory. After all, who can deny that we are chemical creatures, imbued with moods and psychic talents that emerge from the chemical reactions in our brains? The mood-altering drug industry certainly ascribes to this, witness the multi-billion \$ prescription drug market for Ritalin, Prozac, sedatives and the like, not to mention illegal mood-altering molecules. Curiosity about the process that generates neural memory has instigated numerous philosophic and scientific musings [2-11]. For example, Bergson attempted (~1912) to identify "images" without representation, to measure the interval between matter and conscious perception [5]. But he wrote his thesis before the age of codes and coding instigated by Babbage, Turing, Shannon, et al.

And what about emotions? DNA can be considered as a carrier of "genetic memory" but cannot encode emotions. Marr, a more contemporary scientist considered "orthogonalizing a set of key vectors" into higher dimensional space, with "codons" as basic cognitive units (6-8). The use of the term "codon" was unfortunate in that it suggested that memory was encoded as a DNA-type information sequence. Marr's codons and mathematical equations are equivalent to binary-type synaptic signals with no emotive signifiers, totally "demotive". Without dwelling on this overly, it is clear that a codon cannot encode neural memory, as it does not covey an emotive trace of past events, of parent to offspring.

Language presents barriers to understanding the molecular underpinnings of emotions and memory. Explanations become entangled with the conundrums, inferences and paradoxes of the spoken and written word (4). Also, words do not apply to non-verbal animals, who also exhibit "memory". Rather, we would rather consider a "universal" neural memory process that is applicable also to non-verbal neural creatures. But what kind of code can one consider for the "universal" neural net?

We suggest that the issues of neural memory and emotions be addressed chemically, with the same terms used to clarify other biological processes (such as metabolism, photosynthesis, blood coagulation, reproduction, etc.), cognizant of the kinetics and energetics of chemical bonds and mechanisms. Notwithstanding, we were inspired to

undertake such a chemical description of mental phenomena, by comments from two philosophers and one linguist:

- *"No shade of emotion is without bodily reverberations."* - W. James, 1884 [2]
- *"Feeling is the basis of all mental experience."* - S. Langer, 1962 [3]
- *"Since the subject is a physical organism, the system attributed to this must have finite representation."* - N. Chomsky, 1975 [4]

COMPUTER MODEL

The computer chip's "memory material" [12-18] and underlying "information theory" [19-31] establish the concept of a computer memory code and provided models of physically encoding information as holes, pits, magnetic orientation, electron spins, phase changes, distribution of dopants within a matrix, etc. and the design of algorithms to perform (compute) logical operations. For example, the chip can transform and store electronic "input" information into physical correlates, encoded by the disposition of the dopant metals within the chip's matrix, for recall-on-demand, as electronic memory. Electrochemical metallization memory chips have been fabricated from matrices composed of SiO₂, WO₃, TiO₂, etc. Doped with metals (such as Au, Co, Cu, Ni, Pt and W among other) to encode and store information, available for retrieval. It has been suggested that "memristive" devices and networks compute like a brain, suggesting that "they promise to open new directions in neuromorphic architectures and biological studies ". However, the wired connections between electronic components that are proposed to store memory are not analogous to neural synaptic gaps [discussed below in greater detail with regard to the IBM brain chip and the Blue Brain Project, Marx & Gilon, 2017].

Some assume an analogy between computer processing and neural mentation [29-31].

"The brain's analogue mechanism can be simulated through digital ones" [22].

"Computational systems are useful ... to describe brain processes mathematically" [29].

But something is lacking in the mathematical treatment of information with its limited encoding repertoire (0 1). We point out that even at the quantum level, binary formatted information is monotonic, psychically dead, "flavorless", "demotive".

One queries: *By what alchemy could a biochemical process be transmuted into an emotive state?*

To date, nobody has written a mathematical formulation for pain, love, fear, etc., for feelings that are recalled as emotions. By contrast, logical processes can be affected through binary-coded algorithms. For example, pain is felt

physically with muscular contractions, pulse changes and an attendant psychic experience, that are remembered (see conditioning training). But there are no digital codes or algorithms to simulate an emotive state experienced by a neural creature experiencing pain, from worm, to snail, to man [1,32]. Though forcefully suggested by Marr [6-8], emotive states experienced by all neural creatures appear to be beyond the ken of binary coding. One could say:

“There is no room between 0 and 1 for emotions”.

ENCODING/DECODING COGNITIVE INFORMATION (COG-INFO): MOLECULAR RECOGNITION

Enter the chemist/physiologist with a palette of signalling molecules (i.e., metal atoms and neurotransmitters (NTs)) that can elicit emotive states. Modern biologists accept that signalling processes are based on molecular recognition, i.e., binding events [33-40]. Expanding on Darwin [41,42], we expect that the complex neural signals that result in emotive mentation and memory, evolved from the signalling processes expressed by more primitive cells. For example, colonies of bacteria employ a number of “modulators”, small molecules that function as signals to instigate group aggregation and tropic responses; for which they also express cognate receptors on their surfaces, effectively “sensors”. A bacterial colony can be considered as a chemo-dynamic aggregate of individual entities that exchange information to maintain contact and coordinate group responses to the environment, by means of chemical signals (**Table 1**) and cognate sensors.

Table 1. Modulators of bacterial responses (feelings) [43-46].

Acetylcholine (ACh)	
Amino acids (AA) (19)	
cAMP	
Dopamine (DA)	
Epinephrine (Epi)	
Norepinephrine (NE)	
Histamine (H)	
Serotonin (5-HT)	
NO	
Trace metals	
	Universal

BACTERIAL PRECURSOR OF THE NEURAL NET

Continuing in this vein, the brain cab is considered as an assembly of neurons, whose performance must be governed by the laws of chemistry and described by the rules of biology. Its conscious state (of awareness) operates under metabolic conditions and principles similar to those of an aggregate of bacteria. In that the latter evolved from the former, it is worth considering the signalling features of the bacterial aggregate and see how they apply to the neural net.

A bacterial colony feels and responds to its environment by signalling with molecules (bio modulators) that signal and instigate group responses (i.e., feelings) to stimuli (**Table 1**).

Here, the discipline of chemistry with its techniques and theories helps establish biologic facts.

Without delving into the process of cellular evolution but accepting it as an established Darwinian fact, one could consider that neural nets, which evolved from bacteria, employ similar chemo-dynamic signalling modalities. Indeed, analysis revealed that neurons signal one another with the same biomodulators (now called neurotransmitters (NTs)) employed by bacteria (**Table 1**) along with many additional signalling molecules (neuropeptides) (**Table 2**). Here too, the discipline of chemistry helps establish the facts of neurobiology.

A clue to the mechanism of neural memory might reveal an underlying principle applicable to other mental states. Our “leap” of comprehension (of the psychic states achieved by neural nets), is based on the neural morphology (extended,

arborized shape), that permits many connections not only with other neuron, but intimate contacts with the surrounding neural extracellular matrix (nECM), which performs as an archival “memory material”.

Table 2. Neurotransmitters (NTs) modulators of feelings and emotions.

Acetylcholine (ACh)	Universal
Amino acids (AA) (>5)	
cAMP	
Dopamine (DA)	
Epinephrine (Epi)	
Glutamate (Glu)	
Histamine (H)	
Norepinephrine (NE)	
Serotonin (5-HT)	
NO	
Trace metals	
Neuropeptides (> 95)	Specifically Neural
Endocannabinoids (>5)	

An aggregate of bacteria is “conscious”, in that it “feels” environment and responds by chemical signalling. But the bacterial aggregate cannot be considered to be “thoughtful”; it has no memory and cannot recall past stimuli. It responds only to current stimuli with signalling molecules (**Table 1**), sensorially attuned to its environment, conscious in the existential “now”. But memory requires sets of neurons to recall details of past stimuli. An increasingly complex memory talent could only emerge from ever more complex neural structures and signalling (coding) processes. It is not farfetched to suggest that the evolved neural creatures conserved the core mechanisms of bacterial signalling [42-49] and developed new ones (**Table 2**), to perform feats of psychometric signalling, mentation and memory. For example, *C. Elegans*, a primitive organism with 302 neurons has been shown to exhibit memory, the recall of past conditioning experiences (i.e. tapping, electric shock, [32]). Presumably, elegans neurons are encased in their own unique nECM, though characterization has not been reported. It has been established that slime molds are

surrounded by a slime of polyanionic polysaccharides, through which group signalling occurs [50].

Aplysia, a snail with ~20,000 neurons have a memory, can remember past stimuli and act accordingly [1]. The evolving neural systems of more complex animals, with ever more neurons organized into sparse units and specialized anatomic compartments, developed neuropeptides as additional molecular signals pertaining to the evocation of emotions (complex psychic states) (**Table 2**). Concomitantly, cognate receptors developed on the surfaces to detect the nECM-tethered NTs, to be discussed further along our narrative. Characterization of the nECM unique to Aplysia also has not been reported.

The fact that bacterial modulators also serve as modulators of neural signals, emphasizes that neural mentation processes are phyto-chemically related to those of bacterial signalling [44-49]. The modulators (now called NTs) can elicit simultaneous responses from different cells throughout the body or even under cell culture conditions (see [42] for the history of the discovery of NTs). Thus, the multi-tasking

NT “signal” to which a neuron responds is entangled with varied responses of other body cells to the same signal. For example, a list of cell types that respond to ACh would include neurons, as well as heart, liver, kidney, pulmonary and endothelial cells. In a neural creature, they all respond to an administered dose of NT not to be overlooked are the psychic states elicited by the NTs.

NEURONS AND ASTROCYTES (GLIA CELLS)

Though many detailed studies have been performed to characterize astrocytes, neurons and the nECM (cited here and in our previous works), none has clarified the phenomenon of central interest: How is the neural code, which implements mentation and memory, rendered psychically operative by the interaction of neural cells with their surroundings.

The neurons connect to form a signalling network employing both synaptic and non-synaptic (ephaptic or “volume transmission”) signalling modalities [51-58]. The brain’s mental functions are aided by the “housekeeping” performances of astrocytes/glia cells that outnumber the neurons 10-fold [59-67]. The astrocytes have been described as being involved in non-synaptic contacts between neurons. Neuron and glia interactions regulate neuronal biosynthesis of the nECM and transmission through it. Thus, glia cells impact short-term and long-term synaptic connectivity, also correlated to learning and memory.

All these neural cells retain the core chemo dynamic signalling molecules and cognate receptors of bacteria and help the neuron to form contiguous networks coupled to sensors or muscles, as illustrated in **Figure 1**.

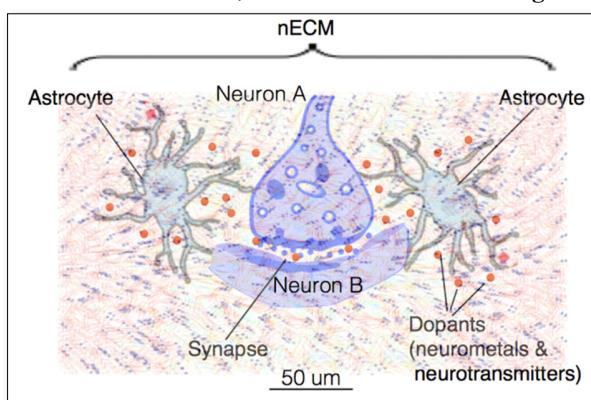


Figure 1. The synapse between 2 neurons clamped by two astrocytes [65-67], ejecting metals and neurotransmitters (colored balls) from vesicles into the synaptic region as well as into the surrounding nECM, the “memory material” (not to scale).

DEFINITIONS

The nECM can be likened to a 3-D lace of organic polymers composed of sulphated glucoseaminoglycans (GAGs) with foci at the metal-binding centres, who’s dielectric and

epitopic aspects is set by the biosynthesis of those sites. It is noteworthy that the process of metal complexation occurs in a nanosecond (10^{-9} s) timeframe.

The term “extracellular space” is misleading, as it implies an empty vacuum around the neurons. Not only are the neurons continuously bathed in a watery (serum, lymph) fluid, they are constrained in a hydrogel lattice comprising a web of glycosaminoglycans (GAGs) in the nECM [68-85] that permits the binding of cationic metals to encode cog-info, as discussed below. Thus, the nECM can be likened to a substrate that has been biosynthesized and treated (i.e., sulphated) so as to prepare metal-binding sites, which serve as nucleating centres for encoding cognitive information involving the binding of NTs [85].

By the term “neuron”, we include combinations of neurons and glia cells that operate in concert to biosynthesize nECM and maintain the neural synaptic and non-synaptic signalling contacts through the nECM, whose performance as a chemo-dynamic “memory material” is manifest as “plasticity”. But the term “synaptic plasticity” (SP) [52, 63, 70] does not serve as a mechanistic explanation of atomic-scale events. Rather, the morphologic changes that are observed in neural dendrites serve to augment the ability of the neuron to interact with the nECM, to recall the code embodied therein. In rats, SP has been observed in a period 5-10 h after the learning experience [11]. But perception occurs in a much shorter time frame (i.e., <1 s). Thus, one must look for faster processes for coding/decoding memory, as discussed below.

The term “imprinting” has been used to describe the recall of young animals to specific stimuli [11]. But unlike the classical meaning of the word “printing” (the transfer of ink to paper), the “imprinting of behavior” is not meant literally but metaphorically i.e., as a learning process presumed to operate on the basis of repeated synaptic connectivity (i.e. SP). But this does not provide a mechanistic understanding of the process of neural recall.

TRIPARTITE MECHANISM OF MEMORY

Consider a tripartite mechanism [86-93], whereby the “neuron” marshals the components available to it. These include the extracellular matrix (nECM in whose lattice it is wrapped) and the dopants (such as metals and NTs), which the neuron accumulates within vesicles, which it ejects. With these, the neuron encodes molecular (rather than cellular) building blocks memory.

A chemographic notation, which describes the chemical basis of the neural memory code as *cuinfo*, is presented (**Figure 2**).

The nECM can be likened to a 3-D lace of organic polymers composed of sulphated glucoseaminoglycans (GAGs) that serve as metal-binding centers. In emotive memory, NTs that complex with the metals within the *cuinfo*, are released from vesicles and are available to form *cuinfo*:NT

complexes. It is noteworthy that the chemical processes of metal complexation occur in a nanosecond (10^{-7}) timeframe.

Thus, it is much faster than neural signalling and would not impede neural communications.

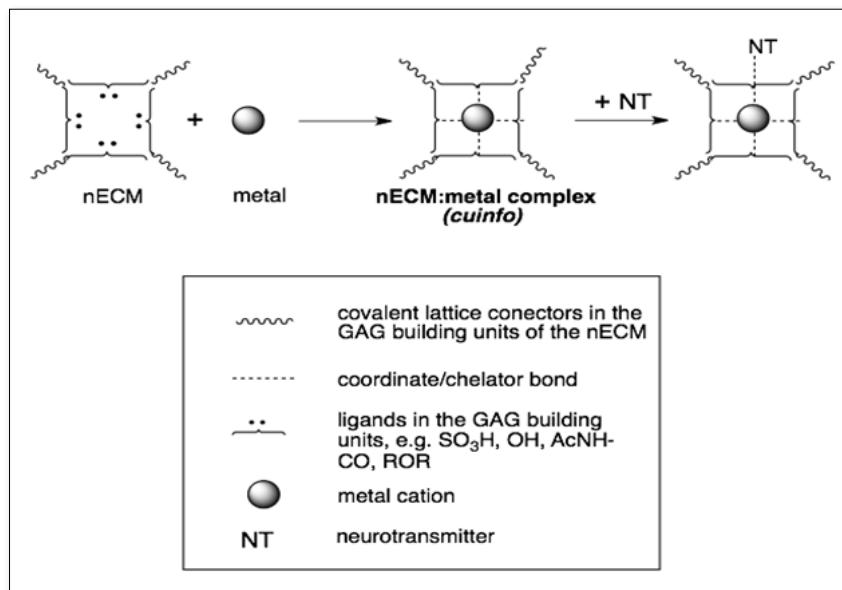


Figure 2. Icons of nECM, with electron-rich, metal-confinement address, capable of encoding cognitive units of information (*cuinfo*, singular, plural), by complexing with metals and neurotransmitters (NT), also modified by derivatizing reactions.

"WRITING" NEURAL MEMORY

We propose that the "writing" of *cuinfo* occurs by neural ejection of vesicles.

The presynaptic neuron (the one that gets an action potential signal) "writes" *cuinfo* by ejecting the content of vesicles [94-118] which contain metals and NTs, to specific addresses within the nECM (**Figure 3A and B**). The only known function of synaptic vesicles is to release neurotransmitters and metals into the nECM [101,102]. The metals are released into the nECM GAGs that have specific pattern of varied planar orientations or densities corresponding to the location of the sulphate groups. Like "inkjet printing" which is based on the piezoelectric dispersion of colored inks as droplets deposited onto paper (**Figure 3C**).

Other workers have suggested that chemical modulators are involved in imprinting memory [113-120], but details of this process need to be clarified. We use the term "neuron" to include the astrocytes (glial cells) that have been shown to release "gliatransmitters", glutamate and ATP [117].

"READING" NEURAL MEMORY

It has been pointed out that cell membranes act as signalling platforms. In that vein, we propose that "reading" of *cuinfo* occurs by virtue of the many sensors embedded within the neural membrane. They detect and decode the various metal-centered complexes contained within the nECM. Based on the literature, we have identified 3 classes of chemo dynamic

sensors embedded within the neural membrane, as discussed below:

1. GPCR receptors [121-150]: These are multimeric proteins (dimers, tetramers, mosaics, aggregates) whose canonical motifs are based on 3 domains: An extracellular domain, extending more than 50Å into the nECM; a transmembrane domain (i.e. 7-helical barrels penetrating the membrane; an intracellular domain, coupled to ATP/GTP metabolism, capable of signalling to its own nucleus as well as to other neurons.
2. The NTs are the molecular equivalents of emotive states, which the GPCRs can detect. The external facet of the moving GPCR sensor (**Figure 4**) is sensitive to pattern of NTs tethered to the *cuinfo* in the nECM. More than 800 distinct types of GPCRs have been identified; neurons express millions of these on their surface (**Table 3**). The seven-transmembrane helix structure of the primitive bacterio-rhodopsin sensor motif is conserved and adapted in all GPCR types (**Figure 5A**).

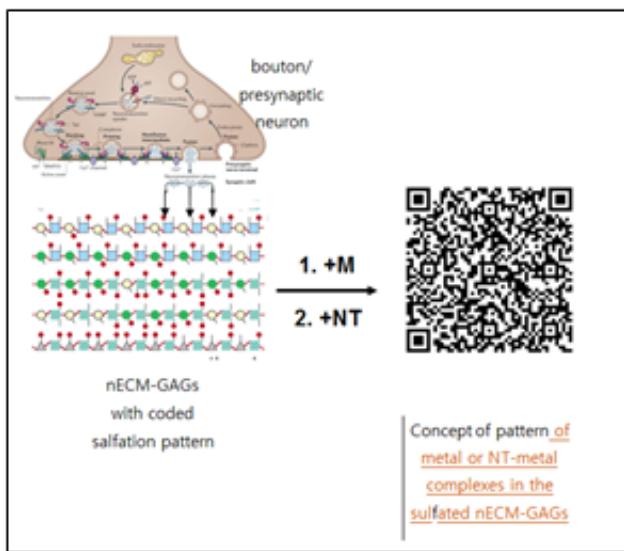
Assuming a $10 \times 10 \text{ \AA}$ size of a *cuinfo*, this would translate into a "reading" of 10^5 to 10^7 *cuinfo*/sec by a single mosaic. Considering that the neuron expresses many thousands of mosaics on its surface, the numbers suggest that the neuron can effectively refresh its recall of many stored memory units.

As the GPCR aggregates are associated with ion channels, they can transduce chemical affinities for tethered ligands (like affinity chromatography [121]), into mini-gating responses related to mini-electric action potentials relating to

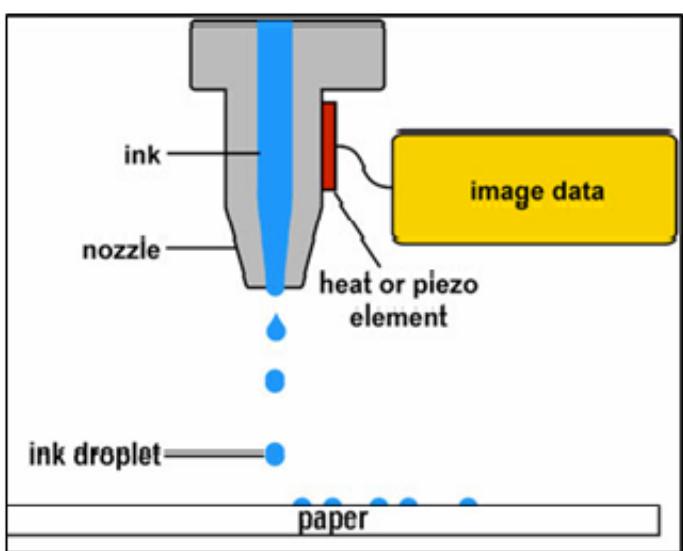
short-term memory. Some are functionally connected to the cell nucleus, to instigate the biosynthesis of new nECM and

proteins, the basis of persistent, long term memory. The GPCRs can perform like dynamic switches, combining and

A.



B.



C.

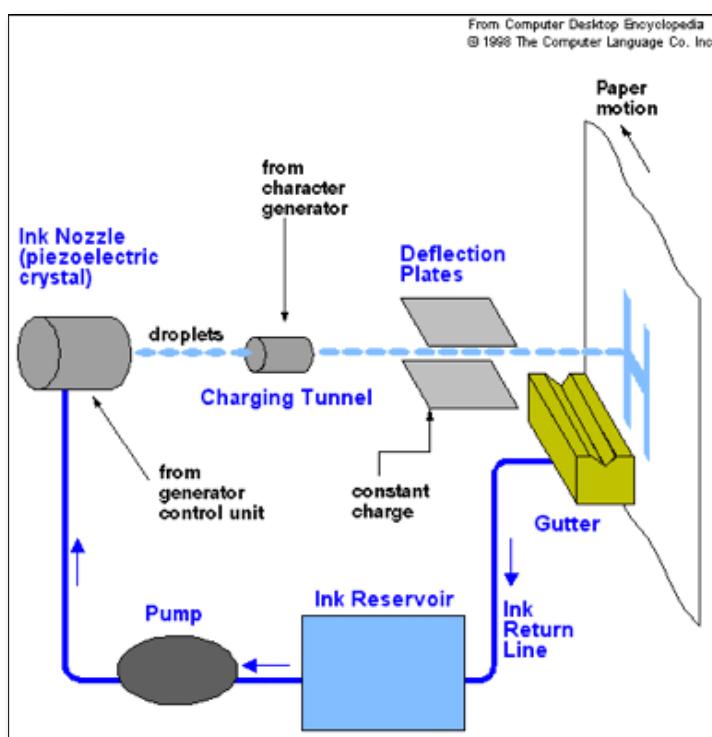


Figure 3. Schematic diagrams of “writing” techniques. **A.** Neuron imprinting *cuinfo* by ejecting the contents of a vesicle containing different metals and NTs into the sulfated nECM enveloping the synapse. **B.** Top view of vesicle distribution on a bouton. **C.** Inkjet printing schema. Each colored ink is delivered from a specific reservoir, ejected and aimed by piezo-electric forces. Regarding the metal handling by the neurons, it has been reported that metallothioneins [119] with metals accumulate in neural vesicles; both could be released into the nECM in a controlled manner.

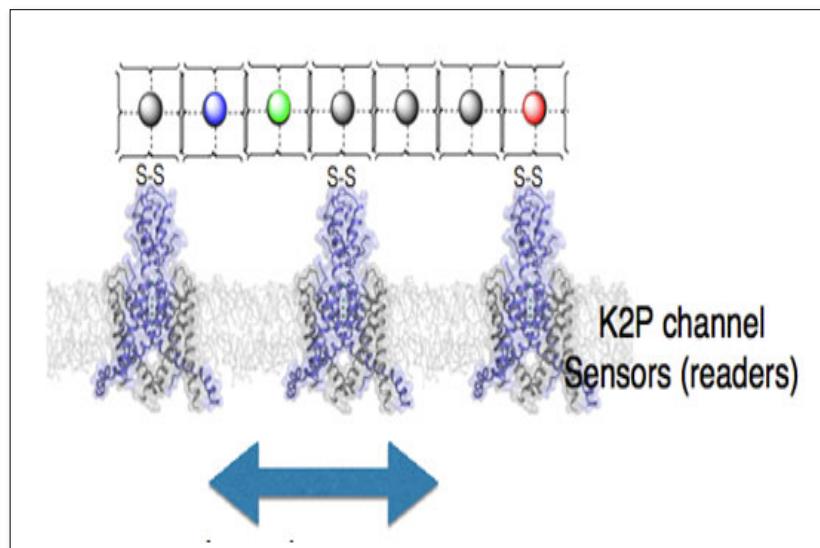


Figure 4. Schematic representation of a K2P channel sensor within membrane of the neuron, “perusing” different cationic moieties of metal-centered cuinfo with its S-S tip, as it traverses the neural membrane, like bar-code readers.

Table 3. Types of receptors to neurotransmitters (NTs).

Class Receptor	Bacteria	Neurons	#Types	Psychic memory
GPCR	Yes	Yes	>800	Emotive
K ⁺ channel	Yes	Yes	~20	Logical
Acetylcholine	Yes	Yes	1	Emotive, attention

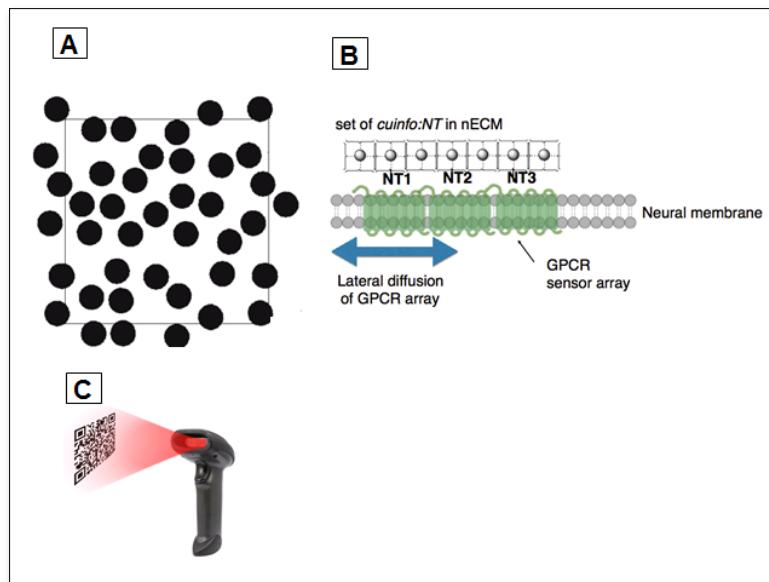


Figure 5 A. Top view of neural surface expressing GPCRs. **B.** Lateral view of GPCR mosaics which exhibit substantial lateral diffusion on the neural membrane, on the order of 10^{-3} to 10^{-1} $\mu\text{m}^2/\text{sec}$ (123-125), which can glancingly recognize (resonate with) cuinfo with tethered NTs. In passing, they recognize the NT and can transmit that decoding event to the neural net. **C.** Electronic code reader-exemplar.

recombining into circuits, diffusing within and through the lipid bilayer surface of the neuron, in continuous contact with the surrounding nECM, “perusing” the exposed *cuinfo* as they traverse along the exposed nECM.

K⁺ Channels [151-158]:

Consider a phonograph needle capable of sensing engraved tracings in a vinyl record with a sharp needle, to transduce tracings into sound (**Figure 6A and B**).

The 2-pore K-channels (K2P) exhibit a structure expected of a sensor. They are organized as 3-domains; an extracellular domain (a sensor cap with an S-S “needle”), a transmembrane region and an intracellular domain. The cap structure extends 35 Å into the extracellular domain and exposes the S-S moiety at its tip to the metals tethered to the *cuinfo* within the nECM.

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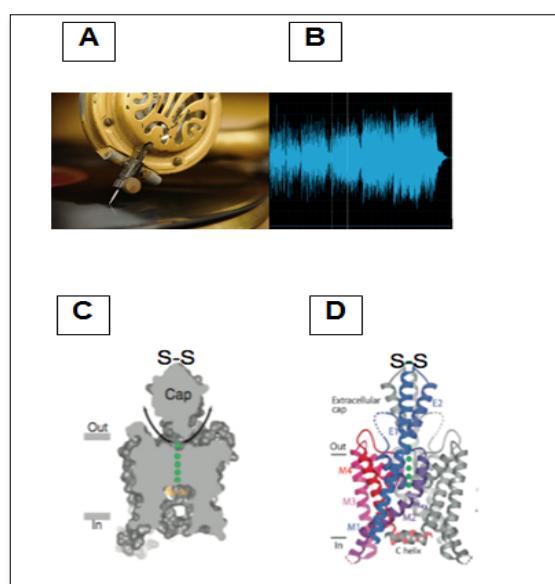


Figure 6 A, B. Phonograph needle on vinyl record, transducing the embossed tracings in the moving vinyl record, detected by needle vibrations piezoelectrically transduced into sound. **C, D.** Two cut-through representation of 2-pore K-channels (K2P). Note that the salient feature of the cap is a S-S moiety, that holds the two halves of the receptor cap together. It is expected that the S-S would be very sensitive to metals, such as those tethered to *cuinfo* [151].

The reactivity of the S-S moiety to metals is well known to chemists. Allosteric flexing induced by the “S-S tip” as it adsorbs/desorbs to a tethered metal cation (of a *cuinfo*) during its traverse of the membrane, could transduce into a mini-gating event, affecting electrical signalling to the neural net, as for example, the tiny spikes around the major

action potential spikes. The S-S bond is relatively weak compared to a C-C bond and could be sensitive to different metals entrapped by the *cuinfo*, as exemplified by the reactions of S-S moieties with soluble metals or metal surfaces (**Figure 4**).

Recent x-ray crystallography findings confirmed this model. The K2P channel was shown to be modulated by a drug (Prozac) which binds to the junction of the channel, where it merges with the membrane of the neuron [156,157]. Interestingly, the side effects of Prozac are loss of memory and changes in psychic states. The binding of Prozac to K2P appears to interfere with the motility of the extracellular region, specifically with the *cuinfo*-reading S-S moiety at the tip of the K2P. Loss of this reading ability is mirrored by forgetting.

Acetylcholine receptors (AChR) [159-167]

The nAChR neuro-receptor is a well-studied ligand-gated ion channel that opens upon acetylcholine binding, and is responsive to the cationic acetylcholine (**Figures 7A and B**).

The exterior facet of the receptor AChR is anionic, presents a 10Å wide, negatively charged face to the outside. This serves to attract the cationic AChol into the channel to become attached to the ligand-binding site. But the negative facet of the AChR could also respond and sense positively charged side chains from NTs tethered to a *cuinfo* through a metal, as illustrated in **Figure 7**.

Its affinity for Ca⁺² and other cationic metals, due to its anionic surface and internal channels, make it capable of sensing and allosterically decoding a *cuinfo* that expresses a cationic ammonium group (R₃NH⁺) (i.e. (e.g. secondary amine in Epi or Arg and Lys neuropeptides) (**Figure 8**). One might also expect that its affinity for the cationic ACh is mirrored by a (milder) response to Arg groups presented by NTs tethered to the nECM. The detected moiety instigates a gated mini-signal to the neural net. The opening and closing of ligand and voltage gated ion channel proteins causes small electrical potential (resistivity) changes on a membrane resulting in mini-electrical signals.

The exterior facet of the receptor AChR is anionic, presents a 10Å wide, negatively charged face to the outside. This serves to attract the cationic AChol into the channel to become attached to the ligand-binding site. But the negative facet of the AChR could also respond to select side chains from NTs tethered to a *cuinfo* through a metal.

SUMMARY OF RECEPTORS/SENSORS

We describe 3 types of membrane-embedded organelles that are involved in chemo dynamic neural “perusing” of the *cog-info* encoded within the nECM around the neuron. There may be other types “perusing” modes.

As regards the history of these receptors, the bacterial system has a number of receptors located within their

surface membranes, as well as ion channels, all which evolved along with the neuron to form the signal sensing

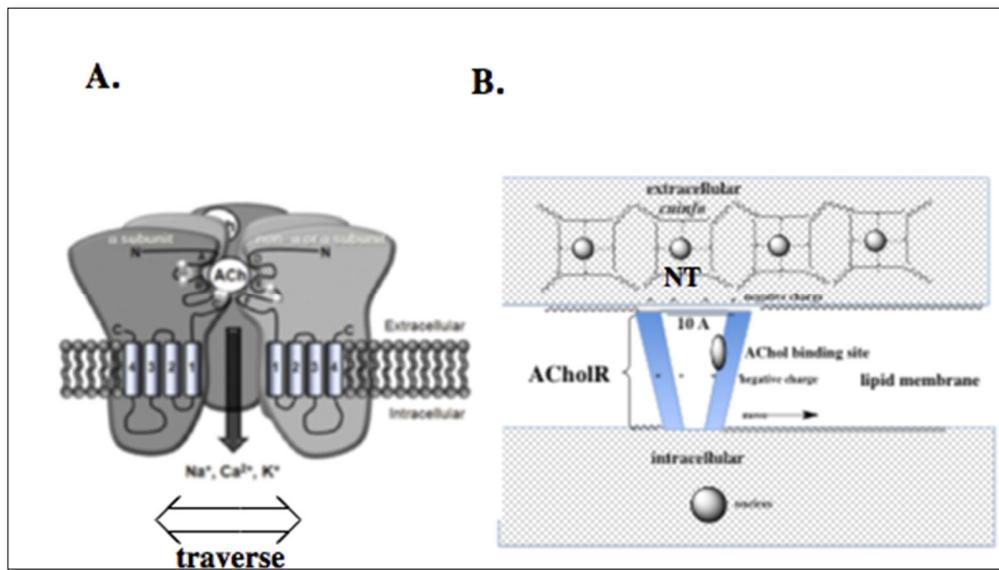


Figure 7 **A.** Representations of the acetylcholine receptor (AChR). The top face is negatively charged, capable of electrostatically attracting cationic acetylcholine to its binding pocket within its channel, and to respond to cations tethered to the nECM. **B.** Schematic representation of the acetylcholine receptor within neural membrane, whose negatively charged face can recognize adsorbed NTs with exposed cationic moieties, such as H⁺: arginine and H⁺: lysine, thereby sensing the *cuinfo* to which it is momentarily exposed.

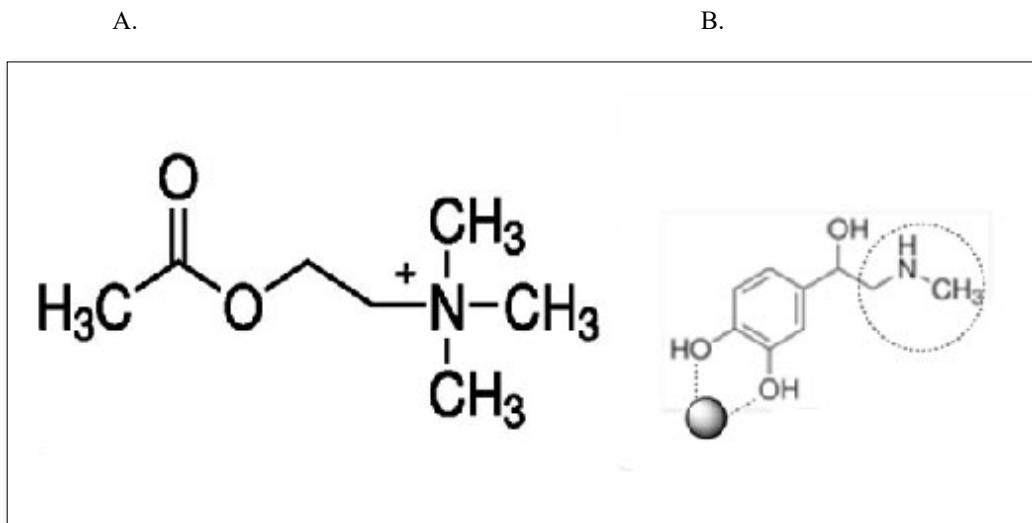


Figure 8 **A.** Acetylcholine structure showing the cationic ammonium entity and the hydrophobic methyl groups. **B.** Epinephrine, chelated to metal tethered to the nECM (not shown). The dotted circle encloses the region which could be sensed by the AChR sensor.

organelles (**Table 3**). Thus, feelings are experienced by neurons via the signalling properties of bio modulators (i.e. NTs) interacting with cognate receptors (**Table 3**), a system that evolved from bacteria (35-42), but adapted and added to, by the neurons to encode, evoke and remember emotive memory.

DISCUSSION

Memory can be classified as a psychic experience instigated by the senses, which is recalled. Some presume that memory is stored in the neuron; others opine that memory is stored as an activity of a neural circuit, though such a "memory

circuit" has not been realized for electronic circuits. Of course, synaptic plasticity (SP) must be involved in the

Table 3. Types of receptors to neurotransmitters (NTs).

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K ⁺ channel	Yes	Yes	~20	Logical
Acetylcholine	Yes	Yes	1	Emotive, attention

various stages of the processing of cognitive information by the neuron. However, the terms SP and its variant "long term potentiation (LTP) do not describe the molecular features by which cog-info is encoded. Rather, it describes the increased ability of the neuron to interact with its surroundings, to decode the cog-info embodied in the nECM and to signal neighboring neurons (see: synaptic contact).

Dogmas of Neurobiology

In keeping with the modern approach to medicine and clinical practice, one cannot simply overlook the explanatory role of biochemistry in elucidating mental processes.

Q: *What are the doctrinal guidelines that a chemist refers to when advocating a possible mechanism regarding psychic neural processes?*

In particular, the dogmas of neurobiology must be questioned, particularly:

- Cajal's model of neural signaling exclusively through synaptic contacts.
- Synaptic plasticity-a la Hebb and Kandel

Q: *How can one describe the molecular features of brain that function to generate memory?*

A: Establish facts – identify critical components/parameters. Then weave the facts into a concept of operation that conforms to the possible chemical interactions available to the neuron. Much has been said about the electrodynamic signalling between synaptically connected neurons. But this is incomplete description. Chemodynamic interactions of the neurons with the nECM, as described by a chemical recognition theory [33-40].

Q: *How does one account for emotions, which have no coding option in the binary world; how are emotions embodied and encoded in the neural system?*

A: Neurotransmitters (NTs) (also called "biomodulators"), are the only molecules in the neuron's repertoire which can affect physiologic reactions and elicit psychic states/emotional responses.

With the exception of acetylcholine which is cationic, most bio modulators contain electron-rich ligands, avid for cationic metals, either free or tethered to a matrix (as in affinity chromatography).

Four criteria for characterizing NTs

1. Biosynthesized in or accumulated by the neuron, stored in vesicles.
2. Released from the vesicles in sufficient quantities to produce a significant (measurable) effect on the postsynaptic cell.
3. Artificial administration of NTs mimics natural release (elicit physiologic and emotive responses).
4. A mechanism exists for NT removal from the synaptic cleft.

Q: *What are we, that we can recapitulate our life experiences through memory?*

A: We are a collection of cells composed of molecules and atoms interacting in a particular way to generate, store and recall psychic experiences, remembered to achieve survival.

The activated neurons "write" by releasing dopant-loaded vesicles into the nECM. The vesicles, which traverse the membrane, are loaded with trace metals and NTs; the neuron controls the location and level of encoders released into the nECM, reminiscent of ink-jet printing of different colors by focused piezo-electric impulses.

Neurons chemo dynamically "read" the nECM via sensor aggregates that move laterally within the membrane lipid bilayer. The nECM structures may be viewed as molecular scaffolds whereby varied planar orientations or densities of the sulphate groups can achieve metal binding interactions which in turn affect affinities for various ligands [85]. Significant inroads have been made in the sequencing of GAGs and encoded sequences. The external facets of the sensors contact facets of the nECM. As they diffuse over the membrane, they allosterically "recognize" the *cuiinfo* at each particular "address" in the nECM; the chemically-induced resonance states of individual neurons are

communicated to neural network via electrodynamic signalling pathways.

One could consider the process in musical terms. The nECM is the “partitura”, the score which the neuron reads with its many dynamic sensors (**Table 3**), like a multi-stringed instrument (**Figure 9**), each string capable of generating a unique tone but resonating with others to generate harmonic overtones. And like music, the “note” must be considered in the context of a set, whose pattern is ‘read’ by the neuron to generate the experience of memory.



Figure 9. Analogy to a neural surface with many sensors, like strings on a harp, each capable generating a unique sound. The music results from the kinetic combinations, resonances and overtones of the excitation of each string. So too, the instigation of the many individual neural receptors on the neural surface results in the “music of mentation”.

The sensors (receptors) perform as biologic “switches which can combine into aggregates (“circuits”) to mentate the individual neuron’s response to chemical signals decoded from the nECM. Some of the sensors are capable of decoding the emotive quality of memory by virtue of their affinity for tethered NTs; others may respond only to metals. Multiples of such aggregates, which are associated with ion-channel gates, traverse the neural surface to “read” the nECM. They effectively process the “chemical algorithms” whereby the neural circuit mentates.

CONCLUSION

Is the search for a universal mechanism of neural memory misguided? Are we forbidden by fear of Descarte’s Mind/Body conundrum? Based on everything we know about the chemical basis of all biological processes, the metaphor of an electronic artefact programmed in binary code is inadequate to describe neural mental activities, as it lacks emotive

qualities (see current discussion of this in Science, April 2018 (174)).

We meld the observations of neuro-morphologists (particularly Triller et al. [124-126] and Vizi [132,133]) with the concepts of the chemist, to present a coherent mechanism that describes how cog-info can be encoded (written), stored and decoded (read). To that end, we envision 4 tasks:

- Define “emotions” with a molecular vocabulary.
- Identify a neural “memory material” wherein persistent memory is stored.
- Describe a neural encoding (writing) process.
- Describe a neural decoding (reading) process.

The tripartite mechanism copes with these points by positing that the neuron forms metal-centered complexes (*cuiinfo*) within the nECM around itself. Expectedly, each metal instigates a unique binding structure with each of the many (>100) NTs and to the nECM. There is much evidence that NTs can elicit physiologic responses as well as emotive states. Thus, it is not farfetched to suggest that each *cuiinfo*: NT presents a unique “ligand pattern” with emotive context, which is sensed by the neural surface (sensors) to reconstruct past experience as memory.

The psychic states achieved by neurons are stored as memory, signalled to the neural net, as schematically presented in **Figure 10**.

The heuristic implications of such a complex, chemo-electric signalling process are manifold. For example, a demonstration of an electrodynamic effect modulated by the interactions of metals with NTs or polysaccharides (as models of the nECM) would augment the credibility of the tripartite mechanism of neural memory. Such work is underway with our collaborators as per the initial reports [168].

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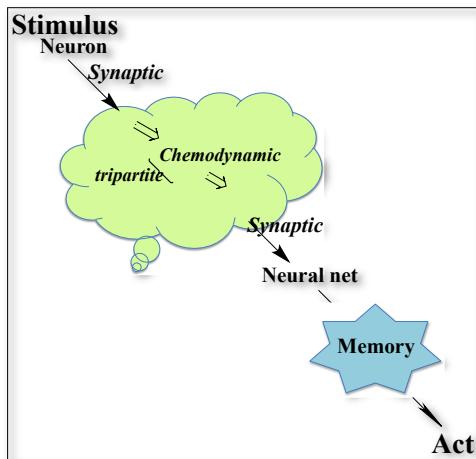


Figure 10. Memory process: Sense stimulus (cog-info) is transmitted synaptically to a brain neuron, which transduces the stimulating synaptic signal into a **chemodynamic** code of a memory event, as *cuiinfo* in the nECM (see tripartite mechanism). This is later sensed by the individual neuron, whose chemo-decoded signals are synaptically transmitted to, and processed (consolidated) **electrodynamically** by, the neural net to achieve a state of mentation manifest as coherent memory, the basis for action. In short, both chemodynamic and electrodynamic modalities are involved in the formation and recall of memory.

CONFLICT OF INTEREST

GM is a founder of MX Biotech Ltd., with the commercial goal to develop new classes of “memory materials” and devices.

CG is emeritus professor of HU, but is active in developing and patenting peptide-based tools for surgery and pharmacology.

Notwithstanding, the ideas forwarded here are scientifically genuine and presented in good faith, without commercial clouding of the concepts expressed herein.

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