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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 which number many thousands per neuron. They perform as dynamic chemo-sensors (reported diffusion: $10^{-1}$ to $10^{-3}$ $um^2$/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 chemo dynamically, 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 "memresistive" 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) | **Universal** |
| Amino acids (AA) (19) | |
| cAMP | |
| Dopamine (DA) | |
| Epinephrine (Epi) | |
| Norepinephrine (NE) | |
| Histamine (H) | |
| Serotonin (5-HT) | |
| **NO** | |
| **Trace metals** | |

## 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 polanionic 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.**

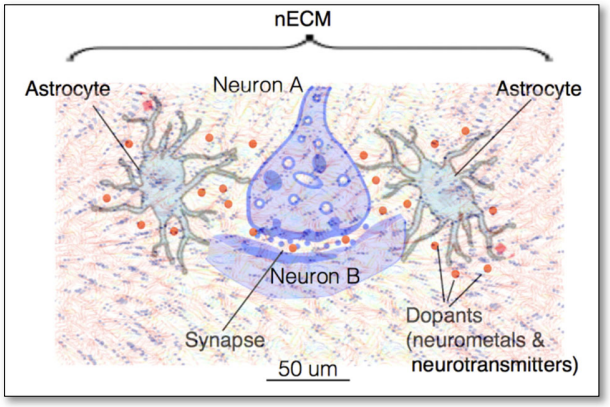



**Figure 1.** The synapse between 2 neurons clamped by two astrocytes [65-67], ejecting metals and neurotransmitters (colored balls) from vesicles into the synaptic region as well as into the surrounding nECM, the "memory material" (not to scale).

## 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) (see above) 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 sulfated 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.

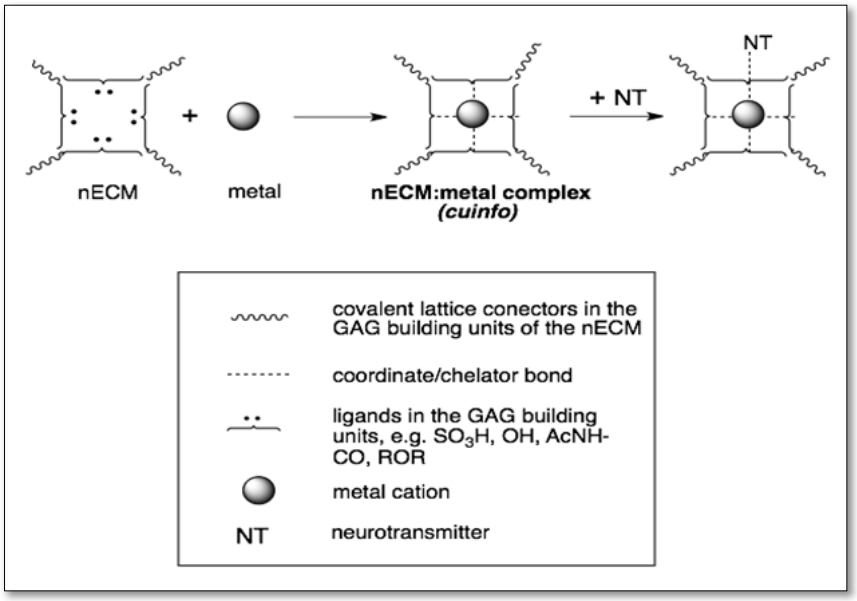



**Figure 2.** Icons of nECM, with electron-rich, metal-confinement address, capable of encoding cognitive units of information (*cuinfo*, singular, plural), by complexing with metals and neurotransmitters (NT), also modified by derivatizing reactions.

**"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.

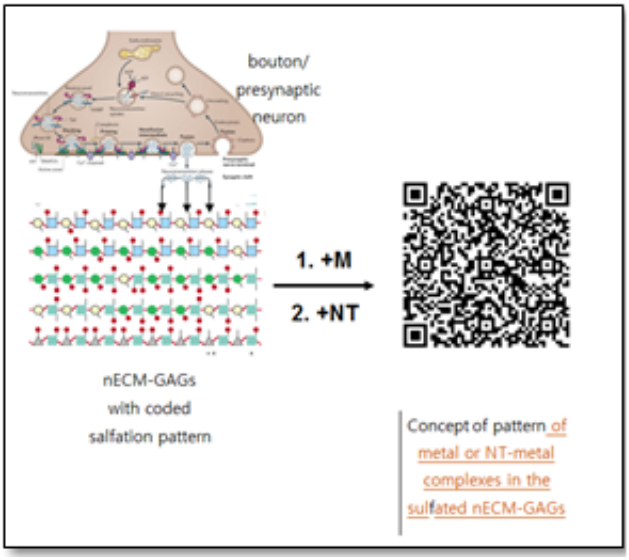
2. The NTs are the molecular equivalents of emotive states, which the GPCRs can detect. The external facet of the moving GPCR sensor **(Figure 4)** is sensitive to pattern of NTs tethered to the *cuinfo* in the nECM. More than 800 distinct types of GPCRs have been identified; neurons express millions 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 10x10Å 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.

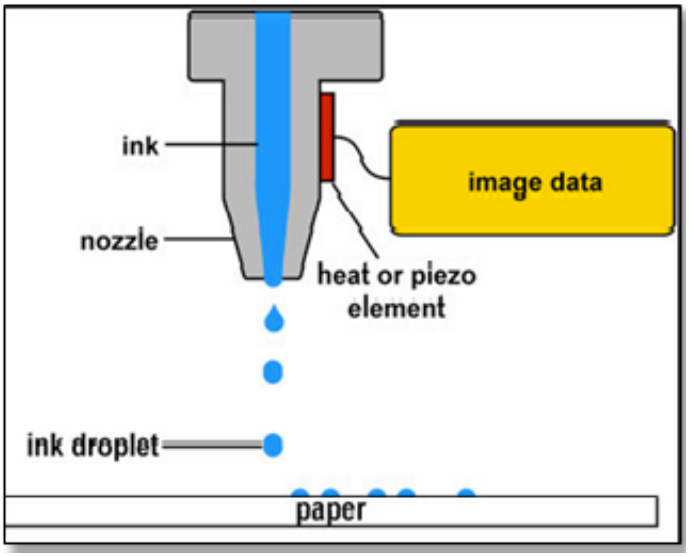
As the GPCR aggregates are associated with ion channels, they can transduce chemical affinities for tethered ligands (like affinity chromatography [121], into mini-gating responses related to mini-electric action potentials relating to

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.

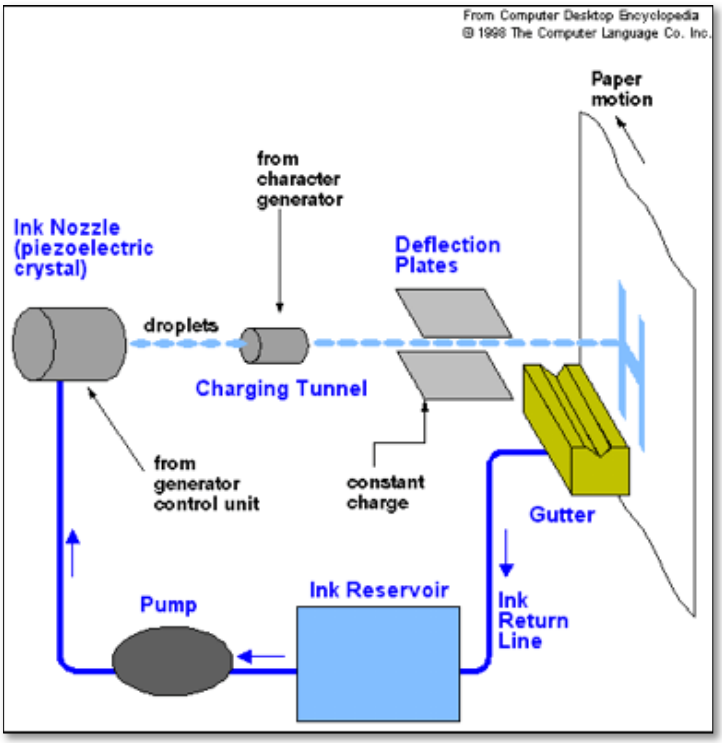



**Figure 3.** Schematic diagrams of "writing" techniques. **A.** Neuron imprinting *cuinfo* by ejecting the contents of a vesicle containing different metals and NTs into the sulfated nECM enveloping the synapse. **B**. Top view of vesicle distribution on a bouton. **C.** Inkjet printing schema. Each 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.

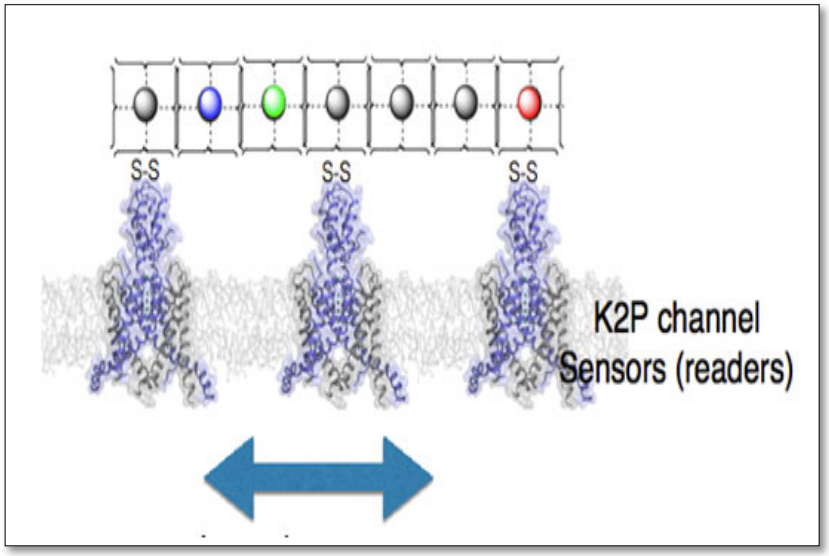



**Figure 4.** Schematic representation of a K2P channel sensor within membrane of the neuron, "perusing" different cationic moieties of metal-centered *cuinfo* with its S-S tip, as it traverses the neural membrane, like bar-code readers.

**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 |

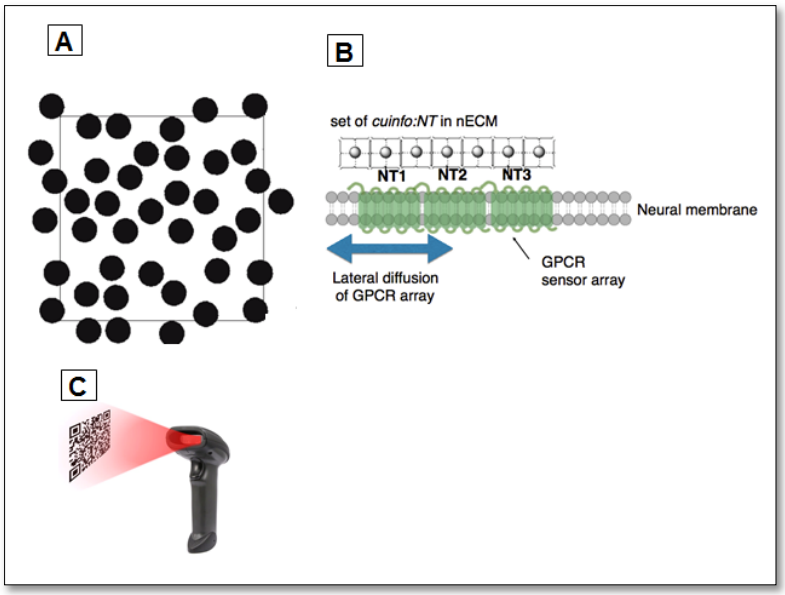



**Figure 5 A.** Top view of neural surface expressing GPCRs. **B.** Lateral view of GPCR mosaics which exhibit substantial lateral diffusion on the neural membrane, on the order of $10^{-3}$ to $10^{-1}$ $um^2$/sec (123-125), which can glancingly recognize (resonate with) *cuinfo* with tethered NTs. 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.

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.

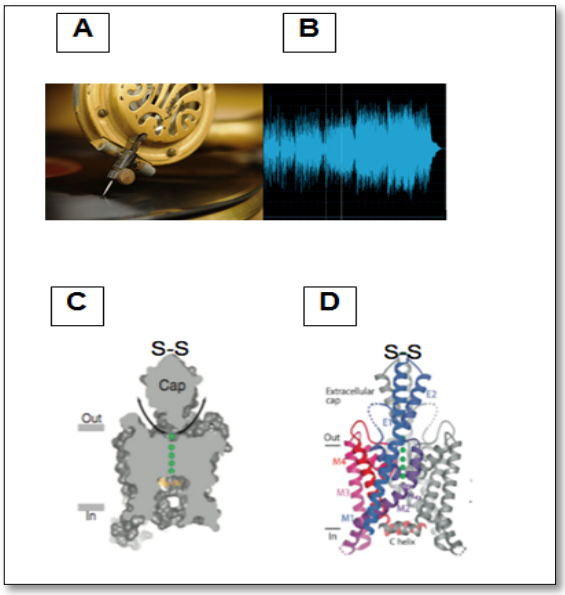



**Figure 6 A, B.** Phonograph needle on vinyl record, transducing the embossed tracings in the moving vinyl record, detected by needle vibrations piezoelectrically transduced into sound. **C. D.** Two cut-through representation of 2-pore K-channels (K2P). Note that the salient feature of the cap is a 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 ($R_3NH^+$) (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

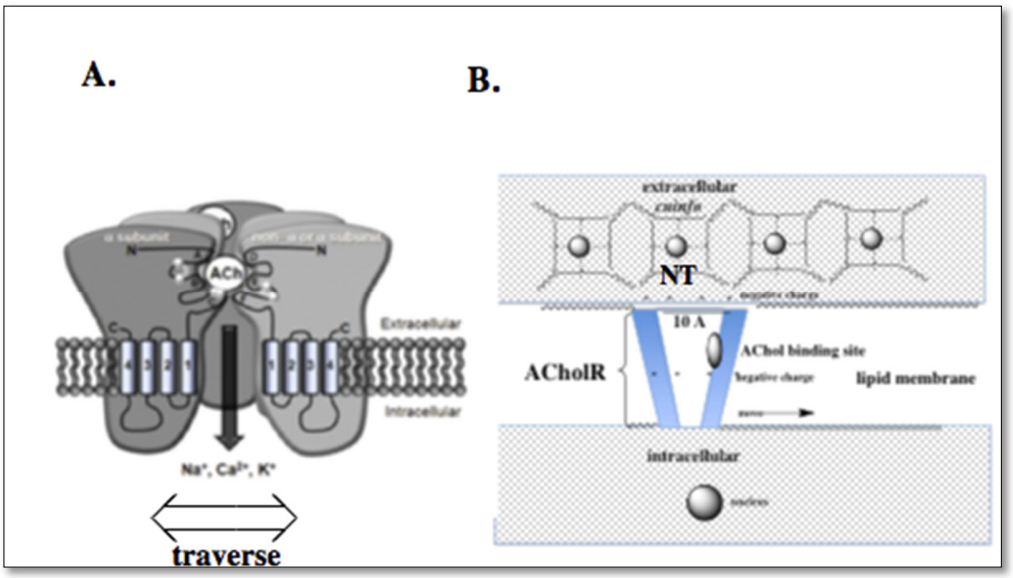



**Figure 7 A.** Representations of the acetylcholine receptor (AChR). The top face is negatively charged, capable of electrostatically attracting cationic acetylcholine to its binding pocket within it channel, and to respond to cations tethered to the nECM. **B**. Schematic representation of the acetylcholine 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.

A. B.

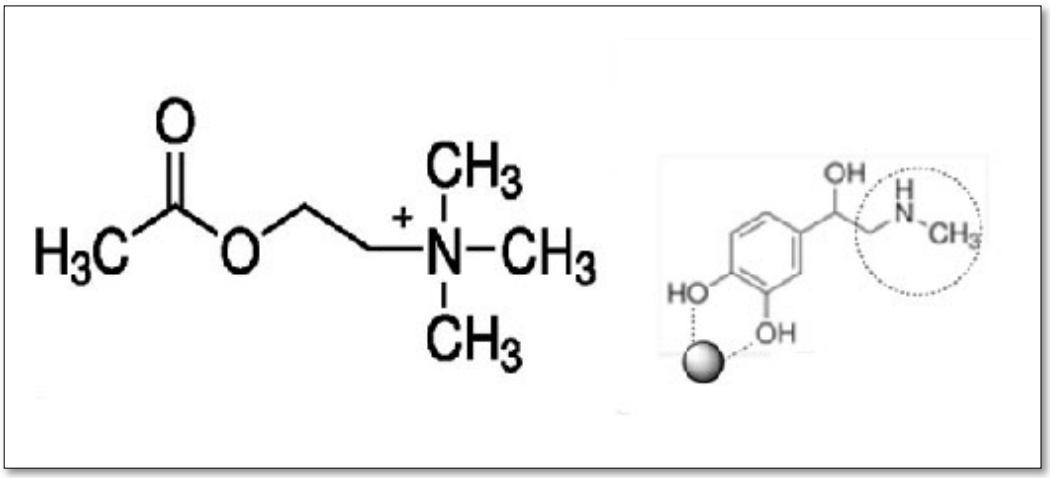



**Figure 8 A.** Acetylcholine structure showing the cationic ammonium entity and the hydrophobic methyl groups. **B.** Epinephrine, chelated to metal tethered to the nECM (not shown). The dotted circle encloses the region which could be sensed by the AChR sensor.

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 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).

**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 |

**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 *cuinfo* 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 (*cuinfo*) 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 *cuinfo*: 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].

## ACKNOWLEGEMENT

(By GM). A memorium to my wife and fan, the artist Georgette Batlle (1940-2009), whose drawings helped me visualize interactions of blood clotting factors modulated by metals, instigating an epiphany regarding psycho-chemical processes. Thanks to friends, Lilly Rivlin (New York, N.Y.) and the late Bill Needle (Eastchester, N.Y.) for their early encouragement and financial support in the period 1980-1984. I appreciate ongoing discussions with Karine Ahouva Leopold (Paris), regarding the distinction between feelings, emotions and behaviour.

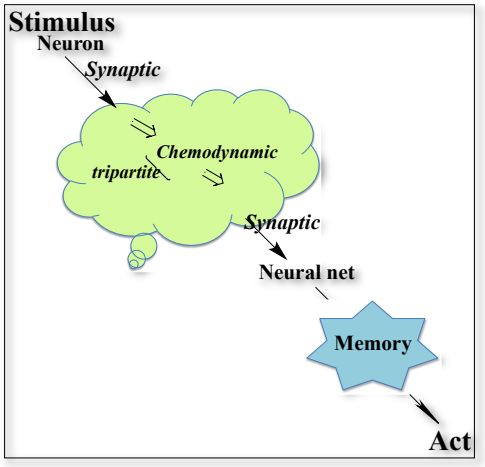



**Figure 10.** Memory process: Sense stimulus (cog-info) is transmitted synaptically to a brain neuron, which transduces the stimulating synaptic signal into a **chemodynamic** code of a memory event, as *cuinfo* in the nECM (see tripartite mechanism). This is later sensed by the individual neuron, whose 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 modalitities 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.

## REFERENCES

1. Kandel ER (2006) In Search of Memory. W.W. Norton & Co., New York.
2. James W (1884) What is an emotion? MIND 9: 188-206.
3. Langer SK (1962) Philosophical Sketches. Johns Hopkins Press, Baltimore, MD.
4. Chomsky N (1975) Reflections on language. Pantheon Books, New York.
5. Bergson H (2004) Matter and memory (translation from French by Paul NM and Palmer WS 1912). Dover Philosophic Classics.
6. Marr D (1970) A theory for cerebral neocortex. Proc R Soc Lond 176: 161-234.
7. Marr D (1971) Simple memory: A theory for archicortex. Philos Trans R Soc Lond B Biol Sci 262: 23-81.
8. Willshaw DJ, Dayan P, Morris RGM (2015) Memory, modelling and Marr: A commentary on Marr (1971) 'Simple memory: A theory for archicortex'. Philos Trans R Soc Lond B Biol Sci 370: 20140383.
9. Dehaene S (2014) Consciousness and the brain. Deciphering how the brain codes our thoughts. Penguin Books, New York.
10. Rosenblum B, Kuttner F (2011) Quantum enigma: Physics encounters consciousness. Oxford University Press, UK.
11. Horn G (2004) Pathways of the past: The imprinting of memory. Nature Rev Neuroscience 5: 108-121.
12. Ventra MD, Pershin YY (2011) Memory materials: A unifying description. Mater Today 14: 584-591.
13. Valov I, Waser R, Jameson JR, Kozicki MN (2011) Electrochemical metallization memories - Fundamentals, applications, prospects. Nanotechnology 22: 254003.
14. Di Ventra M, Pershin YV (2013) Memcomputing: A computing paradigm to store and process information on the same physical platform: 1211.
15. Valov I, Kozicki MN (2013) Cation-based resistance change memory. J Phys D Appl Phys 46: 074005.
16. Seo S, Yoon Y, Lee J, Park Y, Lee H (2013) Nitrogen-doped partially reduced graphene oxide rewritable nonvolatile memory. ACS Nano 7: 3607-3615.
17. Lin WP, Liu SJ, Gong T, Zhao Q, Huang W (2014) Polymer-based resistive memory materials and devices. Adv Mater 26: 570-606.
18. Traversa FL, Di Ventra M (2014) Universal Memcomputing machines. IEEE Trans Neural Netw Learn Syst 26: 2702-2715.
19. Boole G (2005) The laws of thought: The mathematical theories of logic and probabilities 1853. Project Gutenberg.
20. Turing A (1936) On computable numbers, with an application to the Entscheidungs problem. Proc Lond Math Soc 42: 230-265.
21. McCulloch, Pitts WS (1943) A logical calculus of the ideas immanent in nervous activity. Bull Math Biophys 7: 115-133.
22. Neumann JV (1958) The computer and the brain. Yale University Press, New Haven CT.
23. Gleick J (2011) The information. Pantheon Books, New York.
24. Landauer R (1991) Information is physical. Phys Today 44: 93-29.

25. Landauer R (1991) The physical nature of information. Phys Lett A 217: 188-193.
26. Picard R (1997) Affective computing. MIT Press, Boston.
27. Kleine CC (2006) Recognition and simulation of emotions seminar: Human-robot interaction. SoSe Fachbereich Informatik Universitat Dortmund.
28. Levy S (1992) Artificial life. Random house, New York.
29. Guidolin D, Albertin G, Guescini M, Fuxe K, Agnati LF (2011) Central nervous system and computation. Q Rev Biol 86: 265-285.
30. Pockett S (2014) Problems with theories that equate consciousness with information or information processing. Front Syst Neurosci 8: 225.
31. Carleo G, Troyer M (2017) Solving the quantum many-body problem with artificial neural networks. Science 355: 602-606.
32. Ardiel EL, Rankin CH (2010) An elegant mind: Learning and memory in Caenorhabditiselegans. Learn Mem 17: 191-201.
33. Katchalski E (1992) Molecular surface recognition: Determination of geometric fit between proteins and their ligands by correlation techniques. Proc Natl Acad Sci USA 89: 2195-2199.
34. Juliano RI, Haskill S (1993) Signal transduction from extracellular matrix. J Cell Biol 120: 577-585.
35. Lobmaier C, Hawa G, Götzinger M, Wirth M, Pittner F, et al. (2001) Direct monitoring of molecular recognition processes using fluorescence enhancement at colloid-coated microplates. J Mol Recognit 14: 215-222.
36. Gooding JJ, Hibbert DB, Yang W (2001) Electrochemical metal ion sensors. Exploiting amino acids and peptides as recognition elements. Sensors 1.
37. VonKorff M, Steger M (2004) Pharmacophore pattern recognition of small molecular ligands. J Chem Inf Comput Sci 44: 1137-1147.
38. Ma Z, Jacobsen FE, Giedroc DP (2009) Coordination chemistry of bacterial metal transport and sensing. Chem Rev 109: 4644-4681.
39. Marcos V, Stephens AJ, Jaramillo-Garcia J1, Nussbaumer AL, Woltering SL, et al. (2016) Allosteric initiation and regulation of catalysis with a molecular knot. Science 352: 1555-1559.
40. Aschner M (2008) The functional significance of brain metallothioneins. FASEB J 10: 1129-1136.
41. Romanes GJ (1883) Mental evolution in animals with posthumous essay on instinct by Charles Darwin. Kegan, Paul, Trench & Co., London. Nabu Public Domain Reprints.
42. Zakon HH (2012) Adaptive evolution of voltage-gated sodium channels: The first 800 million years. Proc Natl Acad Sci U S A 109: 10619-10625.
43. Valenstein ES (2005) The war of the soups and the sparks. The discovery of neurotransmitters. Columbia University Press, New York.
44. Lefkowitz RJ (2004) Historical review: A brief history and personal retrospective of seven-transmembrane receptors. Trends Pharmacol Sci 25: 413-423.
45. Reith ME (2002) Neurotransmitter transporters: Structure, function and regulation. Springer-Verlag, New York.
46. Mustafa AK, Gadalla MM, Snyder H (2009) Signaling by gasotransmitters. Sci Signal 2.
47. Corringer J, Poitevin F, Prevost M, Sauguet L, Delarue M, et al. (2012) Structure and pharmacology of pentameric receptor channels: From bacteria to brain. Structure 20: 941-956.
48. Zhang Z, Wu J, Yu J, Xiao J (2012) A brief review on the evolution of GPCR: Conservation and diversification. Pharmacol Rev 52: 63-89.
49. Fotiadis D, Qian P, Philippsen A, Bullough PA, Engel A, et al. (2004) Structural analysis of the reaction center light-harvesting complex I photosynthetic core complex of Rhodospirillumrubrum using atomic force microscopy. J Biol Chem 279: 2063-2068.
50. Brown SP, Blackwell HE, Hammer BK (2018) The State of the Union Is Strong: A review of ASM's 6th Conference on Cell-Cell Communication in Bacteria. J Bacteriol 200: e00291-e00318.
51. Koch C, Zador A (1993) The function of dendritic spines: Devices subserving biochemical rather than electrical compartmentalization. Neuroscience 13: 413-422.
52. Stepanyants A, Hof PR, Chklovskii DB (2002) Geometry and structural plasticity of synaptic connectivity. Neuron 34: 275-288.
53. Milo R, Itzkovitz S, Kashtan N, Chklovskii D, Alon U, et al. (2002) Network motifs: Simple building blocks of complex networks. Science 298: 824-827.
54. Fuxe K, Dahlström A, Höistad M, Marcellino D, Jansson A, et al. (2007) From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: Wiring and volume transmission (VT). Brain Res Rev 55: 17-54.
55. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A, et al. (2001) Neuroscience. Sinauer Associates, Sunderland (MA).
56. Brady S, Albers WR, Price D (2011) Basic Neurochemistry: Principles of Molecular, Cellular

and Medical Neurobiology. Elsevier Science, New York.
57. Goyal RK, Chaudhury A (2013) Structure activity relationship of synaptic and junctional neurotransmission. Auton Neurosci 176: 11-13.
58. Cajal R (1995) Histology of the nervous system of man and vertebrae. Oxford University Press.
59. Giaume C, Koulakoff A, Roux L, Holcman D, Rouach N (2010) Astroglial networks: A step further in neuroglial and gliovascular interactions. Nat Rev Neurosci 11: 87-99.
60. Li D, Agulhon C, Schmidt E, Oheim M, Ropert N (2013) New tools for investigating astrocyte-to-neuron communication. Front Cell Neurosci 7: 193-210.
61. Vargova L, Sykova E (2014) Astrocytes and extracellular matrix in extra synaptic volume transmission. Philos Trans R Soc Lond B Biol Sci 369: 20130608.
62. Hirase H, Iwai Y, Takata N, Shinohara Y, Mishima T (2014) Volume transmission signaling via astrocytes. Philos Trans R Soc Lond B Biol Sci 369: 20130604.
63. Haydon PG, Nedergaard M (2015) How do astrocytes participate in neural plasticity? Cold Spring Harb Perspect Biol 7: a020438.
64. Martín R, Bajo-Grañeras R, Moratalla R, Perea G, Araque A (2015) Circuit-specific signaling in astrocyte-neuron networks in basal ganglia pathways. Science 349: 730-734.
65. Stevens B, Muthukumar AK (2016) Differences among astrocytes. Science 351: 813.
66. Perea G, Navarette M, Araque A (2009) Tripartite synapses: Astrocytes process and control synaptic information. Trends Neurosci 32: 421-431.
67. Halassa MM, Fellin T, Haydon PG (2009) Tripartite synapses: Roles for strocytes: Roles for astrocytic purines in control of synaptic physiology and behavior. Neuropharmacol 57: 343-346.
68. Schmitt FO (1962) Macromolecular specificity and biological memory. MIT Press, Cambridge, MA.
69. Bogoch S (1968) The biochemistry of memory: With an inquiry into the function of brain mucoids. Oxford University Press, London.
70. Diyatev A, Schachner M (2003) Extracellular matrix molecules and synaptic plasticity. Nat Rev Neurosci 4: 456-469.
71. Dityatev A, Seidenbecher CI, Schachner M (2010) Compartmentalization from the outside: The extracellular matrix and functional microdomains in the brain. Trends Neurosci 33: 503-512.
72. Kleene G, Schachner M (2004) Glycans and neural cell interactions. Nat Rev Neurosci 5: 195-209.
73. Viapiano MS, Matthews RT (2006) From barriers to bridges: Chondroitin sulfate proteoglycans in neuropathology. Trends Mol Med 12: 488-496.
74. Deepa S, Carulli D, Galtrey C, Rhodes K, et al. (2006) Composition of perineuronal net extracellular matrix in rat brain: A different disaccharide composition for the net-associated proteoglycans. J Biol Chem 281: 17789-17800.
75. Gogolla N, Caroni P, Lüthi A, Herry C (2009) Perineuronal nets protect fear memories from erasure. Science 325: 1258-1261.
76. Avram, Shaposhnikov S, Buiu, C, Mernea M (2014) Chondroitin sulfate proteoglycans: Structure-function relationship with implication in neural development and brain disorders. BioMed Res Int 2014.
77. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK (2016) Extracellular matrix structure. Advanced Drug Delivery Reviews 97: 4-27.
78. Suttkus A, Morawski M, Arendt T (2016) Protective properties of neural extracellular matrix. Mol Neurobiol 53: 73-82.
79. Dzyubenko E, Gottschling C, Faissner A (2016) Neuron-glia interactions in neural plasticity: Contributions of neural extracellular matrix and perineuronal nets. Neural Plast 2016.
80. De Luca C, Papa M (2017) Matrix metalloproteinases, neural extracellular matrix and central nervous system pathology. Prog Mol Biol Translat Sci 14: 167-202.
81. Kamali P, Nicholson C (2013) Brain extracellular space: Geometry, matrix and physiologic importance. Basic Clin Neurosci 4: 282-286.
82. Maroudas A, Weinberg PD, Parker KH, Winlove CP (1988) The distributions and diffusivities of small ions in chondroitin sulphate, hyaluronate and some proteoglycan solutions. Biophys Chem 32: 257-270.
83. Gama CI, Tully SE, Sotogaku N, Rawat M, et al. (2006) Sulfation patterns of glycosaminoglycans encode molecular recognition and activity. Nat Chem Biol 2: 467-474.
84. Miyata S, Nadanaka S, Igarashi M and Kitagawa H (2018) Structural variation of chondroitin sulfate chains contributes to the molecular heterogeneity of perineuronal nets. Front Integr Neurosci 12: 3.
85. Zhang F, Liang X, Beaudet JM, Lee Y, Linhardt RJ (2014) The effects of metal ions on heparin/heparin sulfate-protein interactions. J Biomed Technol Res 1: 1-15.
86. Marx G, Gilon C (2012) The molecular basis of memory. ACS Chem Neurosci 3: 633-642.
87. Marx G, Gilon C (2013) The molecular basis of memory. MBM Part 2: The chemistry of the

tripartite mechanism. ACS Chem Neurosci 4: 983-993.
88. Marx G, Gilon C (2014) The molecular basis of memory. MBM Part 3: Tagging with neurotransmitters. Front Aging Neurosci 6: 58.
89. Marx G, Gilon C (2016) The molecular basis of neural memory. MBM Part 4: The brain is not a computer. Binary computation versus "multinary" mentation. Neurosci Biomed Eng 4: 14-24.
90. Marx G, Gilon C (2016) The molecular basis of neural memory. MBM Part 6: Emotive and rational modes. Int J Neurology Res 2: 259-268.
91. Marx G, Gilon C (2017) The molecular basis of neural memory. MBM Part 7: Artificial intelligence (AI) versus neural intelligence (NI). AIMS Med Sci 4: 254-273.
92. Marx G, Gilon C (2018) The molecular basis of neural memory. Part 10. The sins and redemption of Neurobiology. J Neurol Neurocrit Care 1: 1-7.
93. Kandel ER, Dudai Y, Mayford MR (2014) The molecular and systems biology of memory. Cell 157: 163-186.
94. Segal M (2017) Dendritic spines: Morphological building blocks of memory. Neurobiol Learn Mem 138: 3-9.
95. Cole TB, Wenzel HJ, Kafer KR, Schwartzkroin PA, Palmiter RD (1999) Elimination of zinc from synaptic vesicles in the intact mouse brain by disruption of the ZnT3 gene. Proc Natl Acad Sc USA 96: 1716-1721.
96. Matteoli M, Coco S, Schenk U, Verderio C (2014) Vesicle turnover in developing neurons: How to build a presynaptic terminal. Trends Cell Biol 14: 133-140.
97. Bruns D, Jahn R (1995) Real-time measurement of transmitter release from single synaptic vesicles. Nature 374: 62-65.
98. De-Miguel FF, Leon-Pinzon C, Noguez P, Mendez B (2015) Serotonin release from the neuronal cell body and its long-lasting effects on the nervous system. Philos Trans R Soc Lond B Biol Sci 370.
99. Bruns D, Riedel D, Klingauf J, Jahn R (2000) Quantal release of serotonin. Neuron 28: 205-220.
100. Lasiecka ZM, Winckler B (2011) Mechanisms of polarized membrane trafficking in neurons-Focusing in on endosomes. Mol Cell Neurosci 48: 278-287.
101. Sudhof TC, Rizo J (2011) Synaptic vesicle exocytosis. Cold Spring Harb Perspect Biol 3: a005637.
102. Südhof TC (2013) Neurotransmitter release: The last millisecond in the life of a synaptic vesicle. Neuron 80: 675-690.
103. Trueta C, De-Miguel FF (2013) Extra synaptic exocytosis and its mechanisms: A source of molecules mediating volume transmission in the nervous system. Front Physiol 3: 319.
104. Trueta C, De-Miguel FF (2012) Extrasynaptic exocytosis and its mechanisms: A source of molecules mediating volume transmission in the nervous system. Front Physiol 3: 319.
105. Wilhelm BG, Mandad S, Kröhnert K, Schäfer C, Rammner B, et al. (2014) Composition of isolated synaptic boutons reveals the amounts of vesicle trafficking proteins. Science 344: 1023-1028.
106. Agnati LF, Fuxe (2014) Extracellular-vesicle type of volume transmission and tunnelling-nanotube type of wiring transmission add a new dimension to brain neuro-glial networks. Philos Trans R Soc Lond B Biol Sci 369: 20130505.
107. Prada I, Amin L, Furlan R, Legname G, Verderio C (2016) A new approach to follow a single extracellular vesicle-cell interaction using optical tweezers. Biotechniques 60: 35-41.
108. Farsi Z, Preobraschenski J, van den Bogaart G, Riedel D, Jahn R (2016) Woehler A. Single-vesicle imaging reveals different transport mechanisms between glutamatergic and ABAergic vesicles. Science 351: 981-984.
109. Pan E, Zhang XA, Huang Z, Krezel A, Zhao M, et al. (2011) Vesicular zinc promotes presynaptic and inhibits postsynaptic long-term potentiation of mossy fiber-CA3 synapse. Neuron 71: 1116-1126.
110. Mei Y, Frederickson CJ, Giblin LJ, John HW, Yuliya M, et al. (2011) Sensitive and selective detection of zinc ions in neuronal vesicles using PYDPY1, a simple turn-on dipyrrin. Chem Commun 47: 7107-7109.
111. Kaeser PS, Regehr WG (2014) Molecular mechanisms for synchronous, asynchronous and spontaneous neurotransmitter release. Annu Rev Physiol 76: 333-363.
112. Volknandt W (1995) The synaptic vesicle and its targets. Neuroscience 64: 277-300.
113. Kavalali ET (2015) The mechanisms and functions of spontaneous neurotransmitter release. Nat Rev 16: 5-17.
114. Rizo J, Xu J (2015) The synaptic vesicle release machinery. Annu Rev Biophys 44: 339-367.
115. Davis GW, Muller M (2015). Homeostatic control of presynaptic neurotransmitter release. Ann Rev Physiol 77: 251-270.
116. Borroto-Escuela DO, Agnati LF, Bechter K, Jansson A, Tarakanov A, et al. (2015). The role of transmitter diffusion and flow versus extracellular vesicles in volume transmission in

the brain neural-glial networks. Philos Trans R Soc Lond B Biol Sci: 370.

117. Covelo A, Araque A (2018) Neuronal activity determines distinct gliotransmitter release from a single astrocyte. Elife 7: e32237.
118. Meredith RM, McCabe BJ, Kendrick KM, Horn G (2014) Amino acid neurotransmitter release and learning: A study of visual imprinting. Neuroscience 126: 249-256.
119. Knipp M, Roschitzki GB, Vašák M, Meloni G (2005) Zn7Metallothionein-3 and the synaptic vesicle cycle: Interaction of metallothionein-3 with the small GTPase Rab3A.
120. György C (2011) The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics 2: 187-196.
121. Caron MG, Srinivasan Y, Pitha J, Kociolek K, Lekowitz RJ (1979) Affinity chromatography of the β-adregenic receptor. J Biol Chem 254: 2923-2927.
122. Kroeze WK, Sheffler DJ, Roth RL (2003) G-protein-coupled receptors at a glance. J Cell Science 116: 4867-4869.
123. Agnati LF, Ferre S, Leo G, Lluis G, Carde EI, et al. (2004) On the molecular basis of the receptor mosaic hypothesis of the engram. Cell Mol Neurobiol 24: 501-516.
124. Triller A, Choquet D (2005) Surface trafficking of receptors between synaptic and extra synaptic membranes: "and yet they do move!" Trends Neurosci 28: 133-139.
125. Triller A, Choquet D (2008) New concepts in synaptic biology derived from single-molecule imaging. Neuron 59: 359-374.
126. Choquet D, Triller A (2013) The dynamic synapse. Neuron 80: 691-703.
127. Lundstrom K (2005) Structural genomics of GPCRs. Trends Biotechnol 23: 103-108.
128. Milligan G, Canals M, Pediani JD, Ellis J, Lopez-Gimenez JF (2006) The role of GPCR dimerisation/oligomerisation in receptor signalling. Ernst Schering Found Symp Proc 2: 145-161.
129. Liu JD, Kirti S, Luca Z, Chongguang C, Sean J, et al. (2018) In vivo brain GPCR signalling elucidated by phosphoproteomics. Science 360: eaao4927.
130. Agnati LF, Baluska F, Barlow PW, Guidolin D (2009) Mosaic, self-similarity logic, and biological attraction principles: Three explanatory instruments in biology. Commun Integr Biol 2: 552-563.
131. Worth CL, Kleinau G, Krause G (2009) Comparative sequence and structural analyses of G-protein-coupled receptor crystal structures and implications for molecular models. PloS One 4: e7011.
132. Vizi ES, Fekete A, Karoly R, Mike A (2010) Non-synaptic receptors and transporters involved in brain functions and targets of drug treatment. Br J Pharmacol 160: 785-809.
133. ViziES (2013) Role of high-affinity receptors and membrane transporters in non-synaptic communication and drug action in the central nervous system. Pharmacol Rev 52: 63-89.
134. Yarnitzky T, Levit A, Niv MY (2010) Homology modeling of G-protein-coupled receptors with X-ray structures on the rise. Curr Opin Drug Discov Devel 13: 317-325.
135. Agnati LF, Guidolin D, Albertin G, Trivello E, Ciruela F, et al. (2010) An integrated view on the role of receptor mosaics at perisynaptic level: Focus on adenosine A(2A), dopamine D (2), cannabinoid CB (1) and metabotropic glutamate mGlu(5) receptors. J Recept Signal Transduct Res 30: 355-369.
136. Liebmann C (2011) EGF receptor activation by GPCRs: A universal pathway reveals different versions. Mol Cell Endocrinol 331: 222-231.
137. Kobilka B (2013) The structural basis of G-protein-coupled receptor signaling (nobel lecture). Angew Chem Int Ed Engl 52: 6380-6388.
138. Dulcis D, Jamshidi P, Leutgeb S, Spitzer NC (2013) Neurotransmitter switching in the adult brain regulates behavior. Science 340: 449-453.
139. Stevens RC, Cherezov V, Katritch V, Abagyan R, Kuhn P, et al. (2013) The GPCR Network: A large-scale collaboration to determine human GPCR structure and function. Nat Rev Drug Discov 12: 25-34.
140. Simundza J, Cowin P (2013) Adhesion G-protein-coupled receptors: Elusive hybrids come of age. Cell Commun Adhes 20: 213-225.
141. Meshoulam R, Parker LA (2013) The endocannabinoid system and the brain. Ann Rev Psychol 64: 21-47.
142. Chen L, Duri KL, Gouaux E (2014) X-ray structures of AMPA receptor-cone snail toxin complexes illuminate activation mechanism. Science 345: 1021-1026.
143. Fuxe K, Tarakanov A, Romero Fernandez W, Ferraro L, Tanganelli S, et al. (2014) Diversity and bias through receptor-receptor interactions in GPCR heteroreceptor complexes. Focus on examples from Dopamine D2 receptor heteromerization. Front Endocrinol (Lausanne) 5: 71.
144. Borroto-Escuela DO, Brito I, Romero-Fernandez W, Di Palma M (2014) The G protein-coupled receptor heterodimer network (GPCR-HetNet) and its hub components. Int J Mol Sci 15: 8570-8590.

145. Sabbadin D, Ciancetta A, Moro S (2014) Bridging molecular docking to membrane molecular dynamics to investigate GPCR-ligand recognition: The human a2a adenosine receptor as a key study. J Chem Inf Model 54: 169-183.
146. Alexander SP, Davenport AP, Kelly E, Marrion N, Peters JA, et al. (2015) The concise guide to pharmacology: G protein-coupled receptors. Br J Pharmacol 172: 5744-5869.
147. Dror RO, Mildorf TJ, Hilger D, Manglik A, Borhani DW, et al. (2015) Structural basis for nucleotide exchange in heterotrimeric G proteins. Science 348: 1361-1365.
148. Lee SM, Booe JM, Pioszak AA (2015) Structural insights into ligand recognition and selectivity for classes A, B and C GPCRs. Eur J Pharmacol 763: 196-205.
149. Hurevich M, Talhami A, Shalev DE, Gilon C (2014) Allosteric inhibition of g-protein coupled receptor oligomerization: Strategies and challenges for drug development. Curr Top Med Chem 14: 1842-63.
150. Miller AN, Long SB (2012) Crystal structure of the human two-pore domain potassium channel K2P. Science 335: 432-436.
151. Brohawn SG, del Mármol J, MacKinnon R (2012) Crystal structure of the human K2P TR+ AAK, a lipid- and mechano-sensitive K+ ion channel. Science 335: 436-441.
152. Whorton MR, MacKinnon R (2011) Crystal structure of the mammalian GIRK2 K+ channel and gating regulation by G proteins, PIP2 and sodium. Cell 147: 199-208.
153. Jan LY, Jan YN (1997) Cloned potassium channels from eukaryotes and prokaryotes. Annu Rev Neurosci 20: 91-123.
154. Li W, Aldrich RW (2011) Electrostatic influences of charged inner pore residues on the conductance and gating of small conductance Ca2+ activated K+ channels. Proc Natl Acad Sci USA 108: 5946-5953.
155. Wong DT, Bymaster FP, Engleman EA (1995) Prozac (Fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. Life Sci 57: 411-441.
156. Dong YY, Pike AC, Mackenzie A, McClenaghan C, et al. (2015) K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac. Science 347: 1256-1259.
157. Inbeck HG, Curioni A, Andreoni W (2000) Thiols and disulfides on the Au (111) surface: The headgroup-gold interaction. J Am Chem Soc 122: 3839-3842.
158. Imoto K, Busch C, Sakmann B, Mishina M, Konno T, et al. (1988) Rings of negatively charged amino acids determine the acetylcholine receptor channel conductance. Nature 335: 645-648.
159. Levitt D (1991) General continuum theory for multi-ion channel. Biophys J 59: 271-277.
160. Neumann E (2000) Digression on chemical electromagnetic field effects in membrane signal transduction: Cooperativity paradigm of the acetylcholine receptor. Bioelectrochemistry 52: 43-49.
161. Hasselmo ME (2006) The role of acetylcholine in learning and memory. Curr Opin Neurobiol16: 710-715.
162. Novere NL, Corringer JP, Changeux JP (2002) The diversity of subunit composition in nAChRs (acetylcholine receptors): Evolutionary origins. J Neurobiol 53: 447-456.
163. Changeux JP (2012) Nicotinic acetylcholine receptor: The founding father. J Biol Chem 287: 40207-40215.
164. Youk, H, Lim WA (2014) Secreting and sensing the same molecule allows cells to achieve versatile social behaviors. Science 343: 1242782.
165. Auerbach A (2015) Agonist activation of a nicotinic acetylcholine receptor. Neuropharmacology 96: 150-156.
166. Ho JMI, Bennett MR (2018) Improved memory devices for synthetic cells. Science 360: 150-151.
167. Tadi KK, Alshanski I, Mervinetskiy E, Marx G, Petrou P, et al. (2017) Oxytocin-monolayer based impedimetric biosensor for zinc and copper ions. ACS Omega 2: 8770-8778.
168. Alshanski I, Blaszkiewicz J, Mervinetsky E, Rademann J, Yitzchaik S, et al. (2019) Sulfation patterns of saccharides and heavy metal ion binding. Chem Eur J 25: 1-9.