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Review Article

The Molecular Basis of Neural Memory. Part 10: The Sins and Redemption of Neurobiology

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Abstract

Cajal, the "father" of neurobiology, used Golgi's silver stain to visualize neurons, which he represented as extended, arborized cells with indirect, synaptic contacts to one another (1900–1914). But he represented the neuron as floating in space ("naked neuron"). By contrast, Golgi claimed a Perineural Net (PNN) around the neuron, which Cajal dismissed as a "staining artifact". Notwithstanding, modern analytic and microscope techniques revealed an Extracellular Matrix (nECM) around the neurons, through which non-synaptic signals could pass.

Cajal also enunciated 4 principles of neural signaling. The neurobiologist Hebb [1] interpreted these as "Synaptic Plasticity" (SP). He ascribed the basis of learning and memory to the increased number and functionality of synaptic contacts. Subsequently, Arshavsky [2] accused Hebb of 7 sins", of failing to address many issues critical to modeling neural memory. We note that Hebb and following generations of neurobiologists continued Cajal's "*original sin*", of ignoring the implications of neural shape, thereby overlooking the presence of nECM.

As unction to redeem these sins, we offer a *tripartite* mechanism whereby cognitive units of information (*cuinfo*) are encoded as metal-centered complexes within the nECM, the "memory material" around the neurons. Neurotransmitters (NTs) permit the "chemo-coding" of emotive states, not available to any other coding scheme (Baudot, Braille, binary, trinary, Morse, electronic).

One can no longer evade the inadequacies of the Cajal/Hebb model of exclusive synaptic signaling, which require a rethinking the canons of neurobiology. The novel *tripartite* mechanism, augments the concept of "synaptic plasticity" and provides a chemo-dynamic model of neural coding of memory.

Keywords: *Cognitive information, Metal complexes, Emotions, Neurotransmitters*

Background

"Memory is a mystery as deep as any that psychology can propound."

– William Bateson

"It is obvious that nerve impulse is somehow converted into thought, and that thought can be converted into nerve impulse. And yet, all this throws no light on this strange conversion."

– Roger Penfield

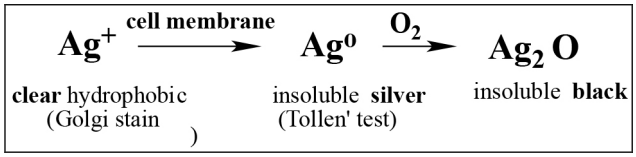
Modern neurobiologists posit that memory results from the cumulative performance of sets of synaptically connected neurons, predicated on the neural model first described by Cajal [1–10]. The terms "Synaptic Plasticity" (SP), "Long Term Potentiation" (LTP), "connectivity" and the like, are currently used to describe the ability to recall. However, such terms lack biochemical definition and do not suggest a coding system. To regain focus, we reexamine the origins of neurobiology.

History

Essentially, Cajal used Golgi's silver stain method to visualize neurons. Cajal saw and drew the neuron as an arborized cell with indirect, synaptic contacts to others. But the neuron's exquisite shape was presented as if it were floating in space, with nothing surrounding it ("naked neuron"). By contrast, Golgi claimed a Perineural Net (PNN) around the neuron, which Cajal dismissed as a "staining artifact".

Technical aside: The chemistry of silver salt underlies its utility as a stain for neurons. It is based on the affinity of soluble Ag^+ for the hydrophobic lipid bilayer of the neural membrane, where it is reduced to insoluble Ag, which oxidizes to form insoluble black Ag_2O [11, 12]. The stain thus reveals neural membrane shape at high b&w definition, effectively a photograph.

Silver Staining Equation



But as the silver stain does not react with polysaccharides of the nECM or most proteins, it did not reveal the nECM web enshrouding the neuron, which remained invisible and unconsidered.

Chemistry aside, Cajal did not infer the reality of the nECM from neural morphology. He did not recognize that the neural shape itself "spoke" about the cell's intimate contact with its surroundings (Figure 1A). It was as if he were a gardner who wanted to understand plant biology, but ignored the soil around the roots or the air around the leaves of the plant (Figure 1B).

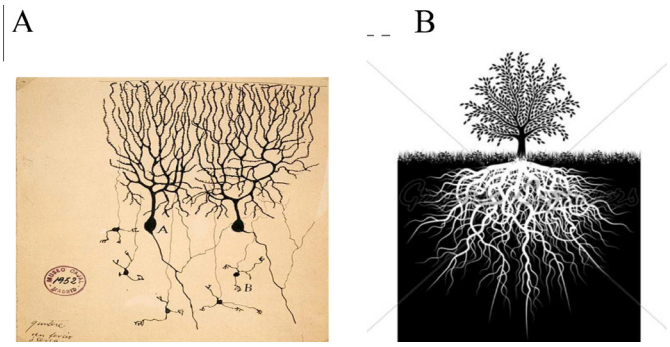


Figure 1. Reverse/ transpose panels A to B and B to A.

A. Cajal drawing (circa ~1911) of a neural net with dendrites extending into the surrounding area, many with no synaptic contact. The nECM is ignored (as "background"), with no function relating to signaling between neurons; hence "naked neurons". B. Contrast-image

Consequently, Cajal ruled out non-synaptic signaling through the nECM. Based on his vision of neural connectivity, he proposed 4 principles of neural signaling.

Cajal's 4 Principles [13]

1. The neuron is the elementary signaling unit of the nervous system.
2. The axon of the neuron communicates with other neurons only at specialized, non-contact regions, gaps called "synapses".
3. A given neuron will only signal with some specific cells but not with others.
4. A neural signal travels in only one direction.

A schematic of Cajal's idea of a neural net is provided in Figure 2 A.

Based on Cajal's principles, McCullogh and Pitts [14] mathematically described sets of synaptically connected neurons, unidirectionally signaling in binary modes (Equation 1).

Equation 1:

$$N_i(z_1) \;.\equiv.\; S\left\{\prod_{m=1}^{q} \sim N_{jm}(z_1) \;.\sum_{\alpha\in K_i} \prod_{\beta\in\alpha} N_{i\beta}(z_1)\right\}$$

Pioneers of the "Information age", von Neumann, Shanon and Schroedinger, attended McCullogh's lecture at the 1948 Hixon Symposium [14, 15]. Ironically, this mathematical approach helped establish the theory and practice of electronic microprocessor memory at the core of modern computer chips. Though impressive, the equations did not throw much light on biological neuron mentation.

Continuing in the "Cajalian" vein, the neurobiologist Hebb [1] also ignored the nECM. He formulated a theory of "Synaptic Plasticity" (SP) wherein the basis of learning and memory was due to the increased number and functionality of neural synaptic contacts. An example of Hebb's mathematical approach (Equation 2), reads:

Equation 2:

$$\frac{\mathrm{d}}{\mathrm{d}\ t} w_{ij} = F\left(w_{ij}; \nu_i, \nu_j\right).$$

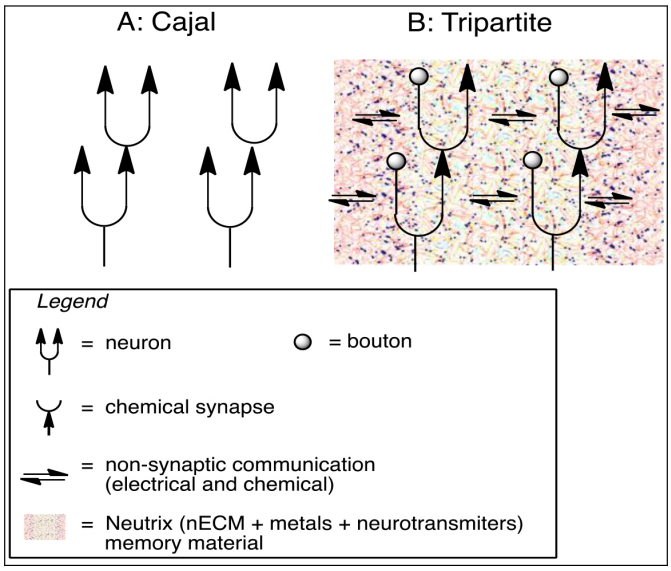


Figure 2. A: Schematic of Cajal's neural net composed of 4 cells in synaptic contact with one another. Note that the neural environment is ignored i.e. "naked" neurons. B. A corrected tripartite schematic of a neural net, enmeshed in a surrounding "neutrix" (nECM + metals and neurotransmitters (NTs)), engaged in non-synaptic, as well as synaptic signaling.

The "Hebbian" model of memory [1, 15–20] ascribed to the following precepts:

1. Memory is represented by the joint activation of (sparse) groups of synaptically connected neurons.
2. Learning results from the strengthening (increased function) of neural synaptic connections, termed plasticity or Long Term Potentiation (LTP).

"Mechanisms of learning and memory reside not in the special properties of the neuron itself, but in the connections it receives and makes with the neural net."

– Kandel [12]

But saying that synaptic connection between neurons are "strengthened" or "tagged" [18] does not describe the molecular details whereby they encode and store persistent memory in accessible form.

Consider the reality of the brain's neural nets. Since the early 1960's and onward,

Golgi's PNN, now called nECM, was rediscovered, characterized by analytic techniques and visualized by Scanning and Transmission Electron Microscopy (SEM and TEM respectively) [20–26]. Today, all neurobiologists admit that neurons are encased in a 3D matrix. Thus, the reality of the nECM has been recognized, but not yet internalized as having functional significance for learning or memory.

Reservations have been raised about the Cajal/Hebb model of neural signaling [2, 26–31]. In particular, it was noted that there are non-synaptic signaling pathways through the ubiquitous extracellular matrix (nECM) around all neurons [32–34]. Still today, most neurobiologists attempt to correlate learning and memory simply with changes of synapse number and functionality, termed Long-Term Potentiation (LTP), and do not account for the non-synaptic dendrites.

Hebb's 7 "Sins"

In the light of the inadequacies of the LTP model, Arashavsky accused Hebb of 7 "sins" [3], of failing to address many issues critical to modeling neural memory.

1. The synaptic plasticity hypothesis cannot explain the long-life persistence of memory.
2. The suggestion, that the same mechanism operates for memory storage and recall, is seriously flawed
3. Memory acquisition and storage have different localizations.
4. "Synaptic" and "system" memory consolidations have different temporal characteristics.
5. Reconsolidation of memory is not "predicted by traditional theories of memory consolidation". Persistent declarative memory, stored in the brain through structural modifications in synaptic connections, "is incompatible with the phenomenon of memory reconsolidation after retrieval".
6. Neurogenesis occurs in the adult brain. Replacing old neurons with new neurons which still retain memory is puzzling; something basic in LPT must be missing.
7. The synaptic plasticity hypothesis does not explain the specific memory impairments present in Alzheimer's disease.

We note other failings:

- The neuron should be described as a polyvalent electro-chemical cell, not a binary (on/off) electrical devise.
- Mathematical descriptions of neural code cannot encode emotions, the basis for mentation.

Doctrinal Guidelines

It is generally accepted that neural mental processing is governed by the laws of chemistry and rules of biology. In today's dogma of neurobiology, Synaptic Plasticity (SP) enshrines the ideas of Cajal and Hebb and many other neurobiologists [35, 36]. But it is hard to devise a synaptic connectivity code that would persist beyond a few seconds and provide emotive context.

One asks: *What can a scientist refer to when advocating a mechanism for coding an emotive event experienced by a neural net?*

Just like "information", "cognitive information" requires a physical embodiment to achieve persistence [36], not simply a dynamic connection between neurons. What is the physicality of the memory trace, the engram?

As we grope for enlightenment, we realize that we require a specific language to comprehend the linkage between the physiology of our bodies and the psychic talents of our brains. To that end, we do not enlist the equations of mathematics [38, 39] or the algorithms of the computer model, but the concepts and iconography of chemistry [40, 41], which has been successfully used to clarify many other, previously mysterious aspects of our biological being, like metabolism, breathing, (i.e. Krebs cycle, hemoglobin) [39], blood coagulation (i.e. cascades of Factors) [42, 43] and reproduction (i.e. DNA ⟶ RNA ⟶ protein) [44].

What are the doctrinal guidelines that a scientist can refer to when advocating a mechanism for a psychic state experienced by the neural net of any creature?

The 7 characteristics and traits that one needs to address include:

1. **Process:** A credible encoding mechanism for neural memory based on generally accepted biochemical principles, with components available to neurons in an aqueous milieu.
2. **Kinetics:** Molecular-scale encoding/decoding process, faster than the rate of neural firing (<100 ms).
3. **Capacity:** Large storage capacity for physically encoding cog-info.
4. **Energy:** Low energy requirements (<400 cal/day).
5. **Storage:** of cog-info for short and long durations.
6. **Loss:** Forgetting as a loss of memory code.
7. **Universality:** Applicable to all animals with neural circuitry.

Tripartite Mechanism of Memory

We propose that the neurons employ their surrounding nECM (Figure 1B) as a "memory material". The diffusible metals and Neurotransmitters (NTs) perform as dopants to encode cognitive information (cog-info), at select addresses within the nECM to form "cognitive units of information" *(cuinfo,* (singular/ plural), metal-centered complexes represented as chemographic icons (Figure 3) detailed by Marx & Gilon [45, 46].

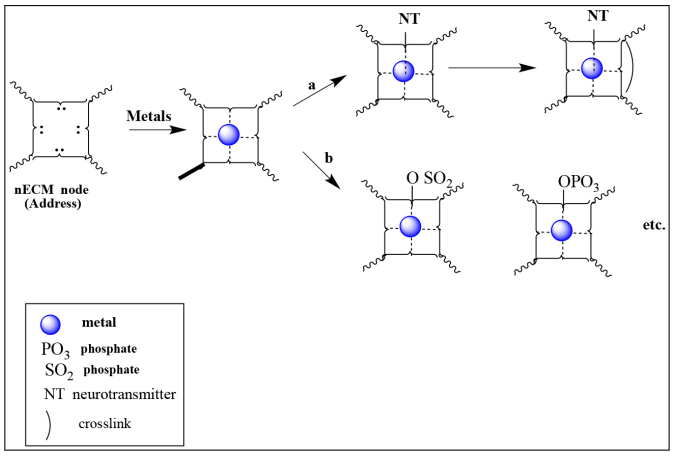


Figure 3. Chemographic representation of the encoding of cog-info. An nECM address can react with a metal resulting in a cuinfo, which can be tagged. The cuinfo can form a ternary complex by binding NT to the metal, sunsequently crosslinked (route a), or the cuinfo can be derivatized by chemical reactions (route b). Both pathways add unique encoding tags. The NTs add psychic dimensions to the cuinfo; the cross-links ensure stability.

Monovalent metals form relatively unstable complexes; polyvalent metals are generally more stable. Some could also engage in redox

(Fenton) reactions, with attendant covalent modifications involving new condensation or cross-linking reactions. Thus, these reactions provide the neuron with a large encoding repertoire. Such a system was contemplated by Fodor [47], but not detailed. We present a chemographic shorthand in Figure 3.

Feelings, Emotions and Memory

The terms "feeling" and "emotion" are often used interchangeably [46]. However, we employ them as distinct terms referring to different physiologic reactions and psychic states:

- "**Feelings**" (often considered psychically [48]), actually relate to body sensations (light, sound, pain, balance, hunger, thirst, etc.) generated by specifc sensors to outside stimuli, which are accompanied by body reactions and corresponding psychic states. They are mediated with biologic modulators, called neurotransmitters (NTs) (Table 1) [49–52]. Astrocytes also release neuroactive molecules (gliotransmitters) to modulate neural signaling [52, 53].

The "meaning" of any stimulus set in memory, is based on its immediate "sensate value", established by NTs. Any sensation (mild or acute) is "felt" physiologically and psychically, concomitant with the release of NTs during neural signaling (Table 1).

Table 1. Neurotransmitters (NTs), which effect both Physiologic reactions and Psychic States

Neurotransmitter (NT)	Physiologic Reactions* (Sensation Feelings)	Psychic Effects!
Biogenic amines (8)	Breathing	Anxiety
Amino acids (>10)	Blinking	Aggression
Neuropeptides (>70)	Blood Pressure	Awareness
Acetylcholine (1)	Cold	Depression
NO (1)	Contraction Muscles	Dreams
Endocannabinoids (>10)	Coughing	Fear
	Crying	Hate
	Dilation of Muscles	Joy
	Dilation of Pupil	Love
	Drooling	Paranoia
	Erection	Sadness
	Evacuation	Sex Drive
	Fever	Sociability
	Goose Bumps	
	Heart Beat	
	Heat	
	Hunger	
	Pain	
	Seeing	
	Smell	
	Thirst	
	Touch	

*No Memory required ! Emotions require memory

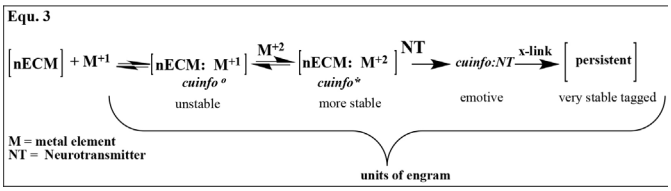
- **"Emotions**" are remembered "feelings", "chemo-coded" with neurotransmitters (NTs), as represented in Figure 3 and detailed elsewhere [45, 46]. NTs can attach to a *cuinfo* via a metal complexation bond and endow it with emotive (subjective) quality.

Accordingly, "feelings" do not require memory, whereas "emotions", psychic states based on recalled feelings, do.

The "chemo-coding" options available to the neural net involve more than (>) 10 diffusible trace metals, >90 NTs and >5 endocannabinoids , collectively >100 "dopants" (Table 1), used by the neuron to encode/decode emotive cog-info within the nECM, with combinatorially explosive encoding options [49–55].

The formation of various sets of *cuinfo* of varying stability presented in equation 3, is the quantal basis for the engram, the trace of memory [56, 57].

Equation 3:



The 1st formed, original unstable *cuinfo* are the templates, which are "transcribed" to various anatomic compartments of the brain, where they are established as stable forms, available for decoding and consolidating into long term, persistent memory.

Discussion

The concepts of "Synaptic Plasticity" (SP) and "long term potentiation" (LTP), have been developed on the basis of Cajal's description of the neuron and its synaptic connections to other neurons. Cajal's model was the basis for the mathematical treatments of neural signaling by McCullogh & Pitts and adopted by Hebbs in his LTP description of neural memory. These have been adopted by the community of neurobiologists and form the basis for most current research in memory. However, serious objections were raised, the Hebbian model was accused of the 7 "sins" enumerated above.

We take a wider view of Hebb's transgressions which stemmed from the limitations of their staining technique. Cajal used Golgi's silver stain, which however, could not stain the nECM around neurons (see above discussion). Thus, he drew "naked neurons", suspended in empty space. Though later generations of neurobiologists (after 1960) could no longer deny the reality of the nECM [57], they still ignored it's possible consequences for neural signaling, as well as the "message of neural shape" (Figure 1A). Most textbooks and current articles still present images of "naked neurons" without qualifying statements about the background. Thus, later generations of neurobiologists perpetuated Cajal's "original sin".

Without belaboring the point, we simply state that the neuron is neither mathematical nor "naked". But it is emotional. We propose that memory is physically encoded as a collection of *cuinfo* within the nECM, the neuron's "memory material" [59–60]. The NTs could be

considered the molecular coding symbols for psychic states [15–19]. Equation 3 describes the formation of sets of *cuinfo* with different NTs, which permit the "chemo- coding" of emotive states not available to any other coding scheme (Baudot, Braille, binary, trinary, Morse). Nor can emotive states be simulated by binary-coded algorithms [61, 62]. We suggest that the earliest formed *cuinfo* become the templates for those formed later, which are transduced and stored in different anatomic compartments of the brain. The consolidation of these dispersed but entangled *cuinfo* into seamless memory is like the cloud computing of the internet. In the interest of space, we defer a more detailed discussion of the neural "read" / "write" mechanisms for another venue.

Paradigm Shift

The acquisition of a paradigm is a sign of maturity in the development of a scientific field [63]. And exchanging one paradigm for another with greater explanatory power, signals greater maturity. One can no longer evade the aforementioned anomalies of the Cajal's and Hebb's model of synaptic signaling, which require atonement, a rethinking of the canons of neurobiology.

The *tripartite* mechanism permits one to redeem the "sins" of Cajal and Hebb, by providing a molecular rationale with 7 virtues, as follows:

7 Virtues of the *tripartite* mechanism

1. Employs available physiologic components (neuron, nECM, metals, NTs).
2. Rapid, little energy requirements (< 400 cal/day human brain).
3. High (near limitless) capacity (combinatorials of Avogadro 10^{23} number).
4. Permits the neural encoding of cog-info, with NTs as emotive signifiers.
5. Describes both short and long term memory in terms of chemical stability.
6. Reveals connection between memory, its loss, and inherited or drug-induced malfunctions.
7. Provides a chemographic representation of cognitive units of information (*cuinfo*), the basic "bits" from which memory is consolidated.

Essentially, we posit that memory is physically embodied by metal-centered complexes employed by the neuron to encode, store and recall *cog-info* in the nECM around the neurons. This mechanism permits neural function in regard to augmented learning and memory, interpreted as SP. The *tripartite* mechanism of neural memory provides a context in which SP is rendered operative as for example, the functioning of "engram neurons" [62].

Conclusion

It is said that God as well as the Devil are in the details. And so too for scientists who desire molecular-scaled details of mental processes. Modern neurobiologists can redeem their "guilt" over Cajal's "original sin" and Hebb's lapses, by confessing that the neuron's shape and environment are relevant to its unique mentation talent, expressed as emotive memory, stored as engrams but without Ryle's ghosts or Augustine's spirits [64–66].

Hebbs assigned increased learning/memory to the phrase "Synaptic Plasticity" (SP), the improved connectivity between two neurons in synaptic contact, which are consolidated by the neural net into coherent recall (learning and remembering). Recent literature also ascribes SP to connectivity between various anatomic compartments (i.e. hippocampus, thalamus, cortex, temporal lobe, etc.) of the brain. Thus, SP has anatomic aspects as well as neural network qualities. But underneath all, lies a molecular-scaled "chemo-coded" reality which must be confessed to atone the past "sins" of neurobiology, those of ignoring the nECM and the "message" of neural shape.

The *tripartite* mechanism complements the observed plasticity of neural nets that become modified as a result of learning. It adds molecular definition to the talent of neural recall. In addition to clarifying the underlying function of the extended neural shape (i.e. exposure to the nECM), it identifies a coding system for emotions in the form of NTs, molecules that elicit both physical reactions and psychic states from neural creatures (Table 1) that must learn and remember to survive.

We continue to mine the rich vein of published literature to cite works which support this *tripartite* mechanism of neural memory with emotive qualities. In following that vein, we employ the concepts and iconography of the chemist, to propose a chemo-coding process that underlies the most obscure qualities of our being, our ability to learn and to forget.

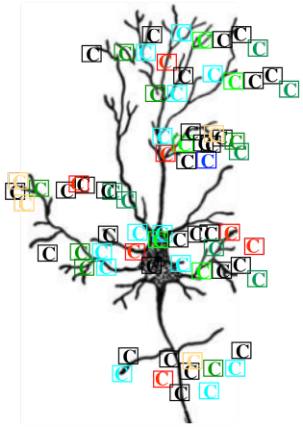


Figure 4. Schematic representation of neuron surrounded by cog-info in the form of cuinfo ( ) with different colors representing different NTs) formed in the nECM .

Acknowledgement

(By GM). A memorium to my wife and fan, the artist Georgette Batlle (1940–2009), whose inspired my graphic approach to molecular reality. 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. Thanks also to Karine Ahouva Leopold (Paris, Jerusalem) for many discussions on emotions and subjective states. Thanks to my brother Rabbi Dr. Tzvi Marx (Amsterdam, Jerusalem) for being a sounding board and for critical reading of the manuscript.

Conflict of Interest

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

CG is a professor emeritus of HUJI. He is active in inventing and developing of peptides and proteins-based drugs.

Not with standing, the ideas forwarded here are scientifically genuine and presented in good faith, without commercial clouding of the concepts expressed here.

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