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Research Article

Expanding on the Tripartite Mechanism of Memory Buttressed with Facts

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Abstract

Mind and body are of a complex unity. The psyche emerges from the physiologic reactions of neural circuits that transduce physical sensibilities into a mental realm.

In a series of essays with many citations, we have proposed a biochemical basis for neural memory, as "bite-size" pieces of cognitive units of information (cuinfo). We described a tripartite mechanism of memory as the process for encoding, storing and decoding cuinfo by the neural circuit, involving the interactions of three physiologic compartments:

- neurons - and associated cells (astrocytes, glia cells). These connect to one another by electrodynamic (synaptic) contacts as well as by chemodynamic (ephaptic) signaling modes.
- nECM- neural extracellular matrix surrounding the neural cells, which serves as a static "memory material".
- dopants - metal cations and neurotransmitters (NTs) as mobile effectors of the neural code. NTs are the molecular signifiers and encoders of emotive states.

The tripartite mechanism is consonant with experimental observations (i.e. facts) as they relate to the connectivity and activities of neurons. We cite numerous experimental works which describe each of these compartments. This mechanism involves only materials available to neurons. Possibly, no collection of facts can serve as "proof", we merely "connect the dots" to establish a sensible rationale for the process of mentation. The tripartite mechanism can be considered as a fulcrum whose turnings reveal a critical facet of the emotive consciousness achieved by the neural net, which functions as the repository of emotive memory.

Keywords: Neurotransmitter/ tripartite mechanism/memory/ signal/ emotion/ neural extracellular matrix

Background

Mind and body are of a complex unity. The psyche emerges from the physiologic reactions of neural circuits that transduce physical sensibilities into a mental realm. However, mental states have been difficult to consider analytically using the usual tools and of the working physicist or the concepts of the mathematician. It seems that a new paradigm must be adopted to address the emergence of mental states from the biochemical workings of neural nets. We really have to think "outside the box".

Some look to "chaos" as revealing a guiding principle for memory [1]. While Sbitnev catagorized memory as resulting from "*memresistive elements* scattered in the brain", he could not describe the biochemical identity of these "elements". In theory, his model of excitable nervous activity could reproduce chaotic modes of neural electrical activity. Notwithstanding, modern biology requires a biochemical description of all biological processes, including the "*memresistive elements*".

The Mental Realm

The "characteristics of mentality are not length, mass, tie or a spatial dimension. Mentality is a realm which emerges from the molecular interactions of neural cells (Table 1). It is a realm that we all experience it but cannot define. The metrics of physics cannot describe it with numeric precision; the computer scientist cannot formulate an appropriate algorithm; the psychologist cannot grasp its molecular essence; the medical clinician can measure its bodily effects (blood pressure, electric conductivity with fMRI, EKG, EEG); the pharmacologists can modulate mentality with drugs, but cannot develop a phenomental vocabulary that captures its chemical identity [2-10].

How can one describe a new talent in terms of the old processes? For example, how can one describe vision to one blind, or music to one deaf? We are caught is a similar quandry. How can one ascribe a mental state to a biochemical process? It seems to involve a phase transition that we experience but don't understand. But it is clear that mentation and memory are equivalent psychic processes generated by the neural net; both are psychic manifestations of neural activity. Thus, we have focused on neural memory as exemplifying the mentality process.

Tripartite mechanism of neural memory [11-35].

Our series of essays has attempted to describe the biochemical basis of neural memory in "bite-size" pieces, with many citations. We describe the biochemical aspects for encoding, storing and decoding of cognitive information (*cog-info*) by neurons, which involves the interactions of three physiologic compartments, namely:

a. Neurons –spindly, elongated cells synaptically connected to others, all suspended in a hydrogel. It also involves helper cells (astrocytes, glia). (Table 1). These connect to one another by electrodynamic (synaptic) contacts as well as by chemodynamic (ephaptic) signaling modes.

b. nECM/PNN- neural extracellular matrix, a static hydrogel lattice comprising glycosaminoglycans (GAGs) enswathing all neurons, also referred to as "neutrix. (Table 2) performing as a "memory material" (Figure 1).

c. Dopants – Diffusible metals and neutrotransmitters neurometals (NMs) within the neutrix, used by the neurons to encode emotive cog-info (Table 3).

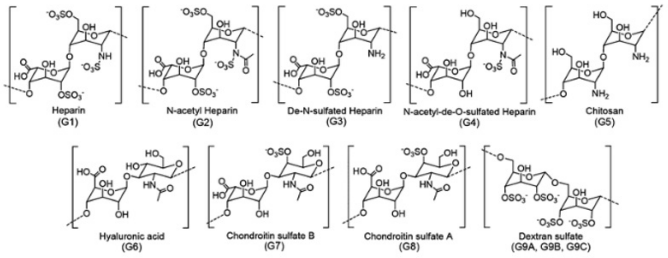

Figure 1. Di-Saccharide isomers showing the stereochemical aspects of different sulfated isomers. Their geometry would affect their specificity for different metal cations and exponentially increase their coding options [36-40].

We developed a chemographic shorthand which permits us to consider the molecular basis for the phenomenon of memory (Figure 2). Though a hexagonal shape more properly represents a saccharide unit (see later), for notational convenience, we adopted a square image with electron pairs to represent the nECM address.

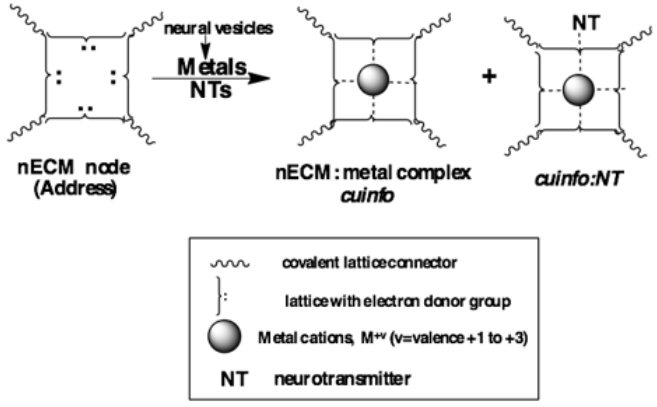

Figure 2. Tripartite mechanism of the chemical formation [11-35] of emotive memory units with a typical NT, of which there are more than 100.

The phenomenon of synaptic plasticity (SP) linking morphological changes in neural microstructures to learning and memory is rendered operational by the above-described tripartite. mechanism.

Facts

Facts which support the proposed tripartite mechanism of memory, are:

1. **Neural types and Morphology** - The splayed shape with large surface area reveals exposure of neurons and other associated cells (Table 1) to the surrounding matrix. These connect to one another by electrodynamic (synaptic) contacts as well as by chemodynamic (ephaptic) signals in the form of neurotransmitters (NTs).
2. **nECM/PNN**, a hydrogel **matrix** of glycosaminoglycans (GAGs) that surrounds all neurons (Table 2) (41-48). It has been suggested that it performs as a "memory material". It has been observed that most dendrites do not establish a synaptic contact with neighboring neurons, but simply terminate in the surrounding nECM/PNN [49,50].
3. **Neurotransmitters (NTs)** - small molecular signals which modulate both physiologic reactions and mental states (Table 3). NTs confer "meaning" or "value" to the emotive states elicited by sensations.
4. **Trace metals** play a key role in forming metal-centered complexes in the nECM/PNN. Their presence in the brain have as detected by atomic absorption, mass spectrometry and neutron activation analysis (AA, LS-MS, NAA) [35]. Mental effects of trace metal deficiency or toxicity on mood and memory is well documented.
5. **Signaling modes**- The neuron employs two modes of signaling, a **synaptic** gap mode, as initially visualized by Cajal and all following neuroscientists ; an **ephaptic** mode, a chemical signaling process based on ejecting vesicles containing metal cations and NTs through the exposed cell membrane (not easily visualized).
6. **The conservation** of signaling molecules from bacteria on upward to evolved primates. All employ the same basic repertoire of signaling molecules. As the neural creatures evolved. these signaling molecules were augmented by neuropeptides and other signaling molecules.

Table 1. Neural cells of the brain

Neurons
-monopolar
- bipolar
- multipolar
-Anaxonic
Glial Cells
Astrocytes - guide neuron development, repair damage, form nECM
Ependymal cells - Form epithelium (ependyma)
Microglia - migrate and clean up molecular debris
Oligodendrocytes and Schwann cells - produce myelin layer
These cells are also crucial for maintaining the homeostasis of the nervous system, forming myelin and providing immune defense.
Microglia - migrate and clean up molecular debris
Oligodendrocytes - form myelin layer
Fibroblasts

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nECM/PNN

The neural extracellular matrix (nECM) and perineuronal nets (PNNs) are complex structures that engulf the neural networks and significantly modulate brain function. The main components are comprised of polyglycans in which various proteins are embedded, as in the following (Table 1):

Table 2. Material Composition of nECM/PNN

1. **Glycosaminoglycans (GAGs):**
   - Hyaluronic Acid (HA) and link proteins
   - Chondroitin Sulfate (CS)
   - Heparan Sulfate (HS):

2. Proteoglycans/Lecticans:
   - Aggrecan
   - Versican
   - Neurocan
   - Brevican

3. Glycoproteins:
   - Tenascins
   - Thrombospondins

4. Metallothioneins:

5. Proteins:
   -Collagen
   -Tenascin
   - Fibronectin

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Table 3. Neurotransmitters (NTs) associated with basic emotions and memory.

Emotion	Emotive Neurotransmitter (NT)
Adrenaline, glutamate, serotonin	Anger
Dopamine, serotonin	Anxiety
Acetylcholine, adrenaline, orexin	Arousal
GABA, glutamate, norepinephrine,	Fear
Amino acids	Appetite, hunger
Aspartate, glutamate, norepinephrine, serotonin, insulin	Joy/depression
Dopamine , epinephrine, glutamate, oxytocin, tryptophan, tyrosine, vasopressin,	Love, sociability
Dopamine, GABA, endorphins, glutamate, glycene, histamine, norepinephrine	Pain
Acetylcholine, dopamine, serotonin, prolactin, pheromone	Sex

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Coding complexity

The neuro-chemical code proposed here has many credible features lacking in others, namely:
a. It is a multi-code (n>100) distinct from the binary code (n=2) of the computer.
b. It provides molecular effectors (i.e. NTs) for encoding emotive states linked to physiologic reactions (35,36).

Essentially, we posit that neurons are surrounded by nECM/PNN, which performs as a neurochemical "memory material" wherein units of memory are encoded as cognitive units of information (cuinfo) and decoded by the neural circuits as emotive memory. This tripartite mechanism is consonant with experimental observations (i.e. facts) as they relate to neural ultrastructure and interactions with the surrounding matrix. This mechanism involves only materials available to neurons (i.e. nECM/PNN, trace metals, NTs).

None of the above constitutes "proof" but it establishes a chain of possibilities. For example, the nECM confers great multiplicity to the possible structures of the polymeric metal-centered complexes which expands the coding options of the neural code (19-24) as exemplified by the structural options of isomeric sulfated di-saccharides (Figure 3).

Sparse Neurons

To establish the neurological basis of memory, some have proposed that select populations of neurons undergo persistent epigenetic changes with experience that permit subsequent reactivation to retrieve experience as a memory trace, an engram (51-53). How select populations of neurons are recruited into a memory trace remains unclear. Gross cellular processes involving epigenetic acetylation of proteins or surfaces with many neurons seem to be too slow to perform mnemotic service. Rather, we suggest that faster biochemical processes (tripartite mechanism), on the order of 10-4 to 10-7 sec are involved in forming a memory trace. For example, the binding of a metal cation with an NT in the nECM are fast, low energy reactions that seem better suited to the kinetic requirements for coding memory acquisition and retrieval. It may be that select groups of neurons are primed for allocation of the neural code imprinted in the nECM. Such neurons could interact with the code embodied in the surrounding nECM performing as a "memory material" servicing those neurons.

Conclusion

The confluence of psychic experience and neuro-chemical processes cannot be ignored. One is a consequence of the other. Intrinsic metabolic processes of the neuron provide the scale whereby the sequence of memory processes can be considered.

The generation of a mental state can be considered as a novel state of being, emerging from ever more complex neural signaling, leading to mentation. An individual neuron cannot achieve a psychic state. The emergence of memory and the evolution of neural systems with higher cognitive talents from simpler cells [54-59] can be considered as a phase transition of caloric energy into the realm of mentality. The complex neural net can generate (instigate) an altered existential state, evidenced by our subjective

experience. No amount of binary computing (Reservoir or otherwise) can mimic the experience of the neural net.

The neuron is like a microprocessor, with multinary modes of processing cognitive information. Analogous to Minkowski's visualization of time as a 4th dimension of space (i.e. space-time), one can conceive of mentation as a new realm of energy related to a phase change emerging from the complex biochemical activity of the neural net (Figure 4).

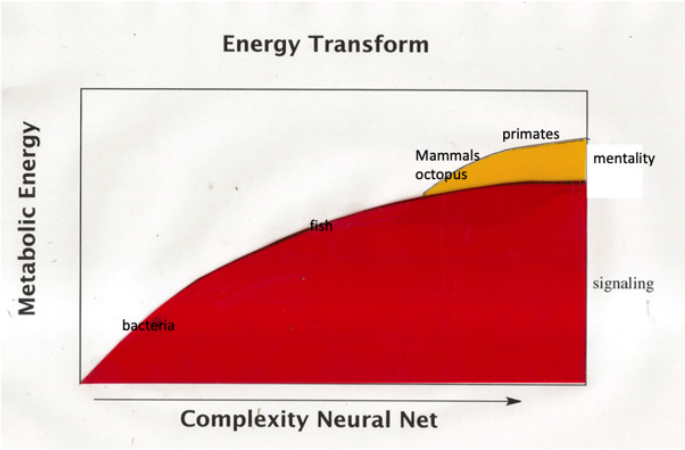

Figure 4. Phase changes corresponding to the onset of mentality from signaling activity of ever more complex beings.

The tripartite mechanism is not just a chemical process, it points to an organizing principle governing emotive mentation. It can be a fulcrum whose turnings reveal memory as a facet of mind. The term "information" does not infer matter or emotion, **or energy** but it implies "recognition". Like the conundrum facing the quantum physicist determining a "fact", the communication scientist requires a conscious entity to recognize information as meaningful data. Without an observer who recognizes, there is neither "fact" nor "information". Even for computers, the value or meaning of any length of data stream (information) is only rendered by the originating programmer. This is much more acute for neural systems which operate on the basis of "subjective consciousness " to recognize and act upon constant stimuli to survive.

The connection between materiality and mentality is inescapable. The ultimate mystery of neurobiology revolves around the issue of how mental states are achieved by a collection of neurons. Memory and thought are manifestations of a single process…. affectations of the play between active neurons and their immediate surroundings.

According to Freeman [57], we may be committing a "category error" [58] by assigning a physical process to an immaterial entity i.e. neural mentality. Notwithstanding, one cannot avoid linking the biochemical activity of the brain to its ability to generate mental talents. Consider the many types of legal and illegal "mind-altering" drugs (mescaline, LSD, cannabis, Prozac, etc.) or those that improve memory and affect mood (Table 4). Also, kinase inhibitors have been explored for their potential role in modulating memory.

Table 4. Drugs that improve memory.

Name	Mechanism	Disease
Donepezil (Aricept)	cholinesterase (ChE) inhibitors	MCI, AD
Galantamine (Razadyne)	cholinesterase (ChE) inhibitors	MCI, AD
Rivastigmine (Exelon)	cholinesterase (ChE) inhibitors	MCI, AD
Memantine (Namenda)	NMDA antagonist	MCI, AD

MCI-
AD- Alzheimer disease

One could consider the neuron as capable of opening a channel from the corporal world of biology to the evanescent realm of thought where the neuron transmutes biochemical processes into a new mental realm, manifest as emotive memory and consciousness.

In that all sentient entities, from bacteria upward to neural creatures, respond to their environment and remember the experience, they can all be considered as "conscious".

However, for our work, we reserve the term" consciousness" for neural creatures that employ neural nets to achieve mentality manifest as active emotive memory.

Thus, we continue our quest to clarify the biochemical processes whereby neural circuits transmute sensory input into persistent emotive memory.

Acknowlegement

(by GM): A memorial to my wife, the artist Georgette Batlle (1940-2009), whose graphic sensibility molded my own. Together, we drew molecular images and protein clotting cascades that shaped my thinking about thinking. I thank friends, Lilly Rivlin (New York, N.Y.) and Ahouva Karine Leopold (Jerusalem, Paris) for their warm encouragement. My daughter (Danae Callaf, Jerusalem) and son (Jonathan, New Jersey) both honored their father in countless ways, for which I thank them.

(CG and GM): Our collaboration exemplifies the sage proverb:
"Iron sharpens iron, and one man sharpens the face of his neighbor" to mean that in a good collaboration, one mind sharpens the abilities of the other. (Mishlei, Proverbs 27:17).

In Conflict of Interest

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