



Mechanism of Memory and Mentation

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Abstract

This article advances a conceptual model outlining a biochemical tripartite mechanism of memory and mentation in the brain. It emphasizes the key contributions of neuronal circuits, astrocyte clusters, the neural extracellular matrix/perineuronal net (nECM/PNN) and metals/neurotransmitters as an integrated framework for encoding, storing, and recalling memory at the molecular level. Unlike models focused solely on electrical signal transmission or binary coding, this narrative posits that memory and conscious experience (mentation) emerge from the chemical interactions of brain cells, their extracellular environment encoded with doping effectors.

The operational components of the tripartite mechanism of memory and mentation are:

- Brain Cells - neuron circuits which communicate with the body (in-out) and glial cell clusters (astrocytes) which perform mental functions.
- Matrix- nECM/PNN, a complex glycosamino-glycan which engulfs all cells and performs as a "memory material" (i.e. library).
- Dopants - metal cations and neurotransmitters (NTs) which encode experience within the nECM/PNN, effectively using both dopants to encode "emotive memory".

The tripartite mechanism of biochemical memory is presented chemographically with a chemical shorthand that summarizes the molecular features of recalled emotive states. It is consonant with the material options available to the brain cells. We review recent evidence on astrocyte-mediated information processing, nECM/PNN structure-function relationships and the pivotal roles of metal cations and dopants in molecular memory encoding.

Theoretical implications of the proposed tripartite mechanism span neuroscience, cognitive science, and educational research, offering new perspectives on how molecular processes shape emotional memory, learning and consciousness. The model encourages future research on the molecular dynamics of the nECM/PNN and the translational potential of targeting astrocyte-matrix interactions for clinical mental health interventions.

Keywords: Neural Code; Tripartite Mechanism; Memory; Cognitive Information; Mentation

Background

Modern efforts to study the brain's ability to control the body's behavior have either modeled themselves on the binary computer code (0 1) [1-11] or focused on the synaptic signaling between neurons [12-20]. It subsumes a process whereby synaptic contacts between neurons, originally observed by Cajal, transmit cognitive information (cog-info) via electrical signals. Hebb further proposed that the synaptic contacts have variable signal strength which are the basis of a neural code [7]. The neural circuitry somehow transduces the sensory signals into emotive memory and consciousness. But the identity of the neural code and the process by which it generates emotive states and consciousness remain obscure.

Taking a broad view of the neuro-scientific enterprise, we list the materials and fields that constitute physical, chemical and biological reality (Lists 1, 2, 3).

List 1. Forces and fields concerning physics

- Gravity, weight
- Mass (atoms and subatomic components)
- Heat
- Force/Momentum
- Electro-magnetism
- Light
- Strong and weak nuclear forces

List 2. Materials and reactions concerning chemistry

- Composition (atoms, molecules, weights)
- Reactions (synthesis, degradation, kinetics)
- Energy of reactions (exothermic, endothermic, equilibrium)
- Stereochemistry (isomers, enantiomers, conformers)

List 3. Processes concerning biology and physiology

- Homeostasis (regulation of internal environment to maintain stability)
- Signal transduction via electrodynamic processes whereby cells respond to external signals
- Signal transduction via chemodynamic processes
- Metabolism (energy management, anabolism and catabolism).
- Growth (increase in size and number of cells)

- Response to external stimuli (reaction to environment)
- Reproduction (production of offspring)
- Respiration (energy extraction from organic molecules)
- Photosynthesis (conversion of light energy to chemical energy in plants)
- Protein synthesis (transcription and translation of genetic material)
- DNA replication (copying genetic material for cell division)
- Transport (movement of molecules within or between cells)
- Excretion (removal of waste)
- Mentality- achievement of psychic states manifest as memory and emotive experiential states

How brain cells achieve mental states is the "grand conundrum" of neurobiology. It has mystified thinkers of all ages. None of the common concepts of physics or chemistry help unravel the mystery of mentation. It has engaged the attention of physicists of all stripes (i.e. classical, quantum, electro-dynamic, thermodynamic, mathematics and information gurus). As well, it has ensnared the interests of philosophers, theologians and linguists [21-31].

It can be considered as a phase change, of caloric energy transcended into mentality, a conversion not obviously described by the laws of thermodynamics. Most neuroscientists focused on "signaling" between neurons but did not delve into the chemistry of "mentality". They were enamored by the "synaptic contacts" between neurons first visualized by Cajal with the Golgi silver stain. They ascribe to a Hebbian code enabled by variable strength synaptic contacts ([7,8], see Connectome Project). Below and in our previously published works (Marx and Gilon, 2012-2025), we discuss their theoretic models and point out that their lack is due to ignoring the reality of brain cell morphology, composition and environment.

Methodology and conceptual framework

Main mechanism and scientific rationale

The central mechanistic proposition is that memory and mentation arise from a coordinated tripartite process, as enumerated:

- Neuronal circuits carry input signals from sensory systems; cognitive information (cog-info).

- Astrocyte clusters, in dense interaction with neuronal networks within the brain which encode, retrieve and interpret, cog-info for meaning (value);
- The nECM/PNN + Dopants provides a chemically addressable molecular matrix where cog-info encoded by dopants is stored as stable, retrievable biochemical “engrams”.

In this model, metal cations (such as Zn^{2+} , Ca^{2+} , Mg^{2+} , Cu^{2+} , Mn^{2+} , etc) and a diverse array of neurotransmitters act as mobile dopants—physically and chemically binding to the elaborate sugar and protein matrix of the nECM/PNN. These interactions encode specific emotive and cognitive experiences as molecular signatures, creating a durable memory trace. The nECM/PNN’s sulfation and glycan patterns constitute a spatial and chemical address system for coding, while astrocytes rapidly write and read information to and from these addresses in response to neural activity and behavioral context.

This process, which we term the “tripartite mechanism,” is supported by recent empirical evidence regarding:

- Astrocytic involvement in memory and cognition,
- Ultrastructural mapping of the nECM/PNN,
- The regulatory and encoding roles of metal ions and neurotransmitters in synaptic and perisynaptic environments.

The framework recognizes that a mental “phase change”—the emergence of subjective experience from physical and biochemical substrate—is not yet fully understood by physics or computer science, but can be meaningfully explored through an integrated biochemical-neurobiological model.

Tripartite mechanism [32-43]

We attempt to harness the discipline of chemistry coupled to biology to suggest a mechanism grounded in the resources available to the brain cell clusters, which transcend caloric energy into mentality, manifest as memory and emotive states. Thus, psyche emerges from the ability of brain cells to transduce physical sensibilities and caloric energy into a mental realm. The biochemical processes that the brain cells perform can be described by a tripartite mechanism of memory as described below.

The chemographic shorthand for the tripartite mechanism permits us to consider a molecular basis for the phenomenon of memory. Though a hexagonal shape more properly represents a saccharide unit, for notational convenience, we adopted a square image with electron pairs, to represent the nECM “address” (Figure 1).

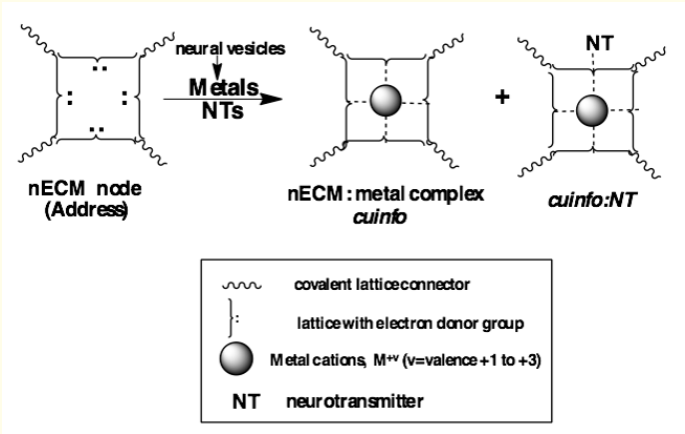


Figure 1: Tripartite mechanism of the chemical formation of emotive memory units with metal cations and NTs, of which there are more than 5 and 100 respectively ($n_{\text{metal}} > 5$; $n_{\text{NT}} > 100$).

Major components

Brain cells

As to cells, most attention has been focused on neurons, particularly on their many synaptic contacts (see Connectome Projects). Neurons connect to sense organs and to one another by electrodynamic synaptic contacts. These elongated cells permit long distance signaling between the brain and the body's distal sensors, muscles and organs. Modern technologies are available to detect the electrical signaling (see EEG, EKG) like a metal circuit board. The term "neural network" has been appropriated by computerists to describe the many circuit connections in their chips, though this is far from biologic reality.

Rather, we draw attention to glial cells (astrocytes), which outnumber the neurons to which they are attached [44-57]. All are enmeshed in the glycosamine (nECM/PNN) lattice [58-66]. Astrocytes as well as neurons emit and respond to different neurotransmitters (NTs) elicited by sensing neurons, using them to encode the emotive context. Together, they comprise a neural circuit which senses the environment, and encodes this via astrocytes into the nECM/PNN, to remember and mentate on recalled memory to determine action (Figure 2 A,B).

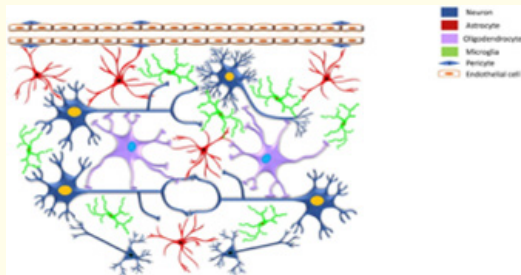


Figure 2A: Circuit of elongated neurons and rounder astrocytes in synaptic and membranal contact with one another. Note that this representation is missing the nECM/PNN matrix [49-57] in which all cells are encased (see Figure 2B. below).

Matrix: Realizing nECM/PNN [55-62]

Figure 2B. An overlay showing a schematic representation the nECM/PNN (see below) engulfing the neuron-astrocyte networks. Thereby, tripartite memory is readily available to the astrocyte clusters that decode memory and mentate to determine action.

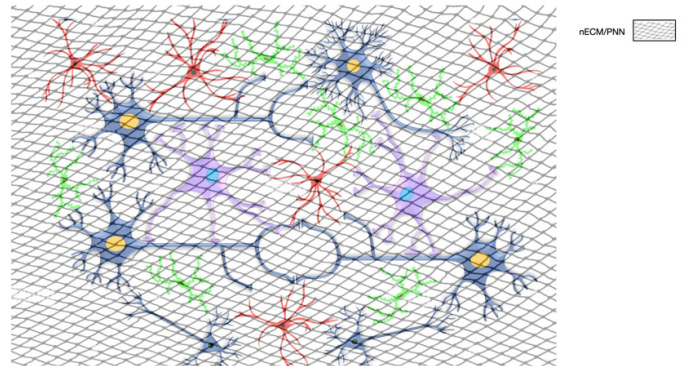


Figure 2B: Brain cells all encased in nECM/PNN.

Histologically, the nECM/PNN was not visualized by the Golgi stain used by Cajal, only synaptic neuron circuits were visualized [53-59], the nECM/PNN was invisible until later techniques were developed. Later work with periodate PAS stains revealed a web of glycosaminoglycans (GAGs) around the brain cells, termed PNN by Golgi but now termed neural extracellular matrix (nECM) [55-62]. The PAS staining method of nECM was based on the oxidation of vicinal OH groups in the constituent saccharide units to generate two aldehyde groups. The addition of a clear Schiff base derivatized the aldehydes, colored them and rendered the visualized nECM purple or red (detailed in Marx and Gilon, [37]). Subsequently, two electron microscopy techniques (SEM, TEM) further revealed details of the nECM/PNN ultrastructure. The saccharide geometry (Figure 3) affects the binding of metal cations and NTs. This complex gel surrounding the neural cells serves as a static and stable "memory material". It stores the molecular embodiment of the "en-gram", the physical memory trace first proposed by Semon [21].

Dopants

Metal cations (such as Zn^{2+} , Ca^{2+} , Mg^{2+} , Cu^{2+} , Mn^{2+} , etc) and neurotransmitters (NTs), mobile effectors of the neural code. Note that the NTs are the molecular signifiers and encoders of emotive states.

Concomitant to affecting mental states, the NTs elicit physiologic reactions in the body. These dopants are inserted into the nECM/PNN, which effectively performs as the "neural code" effectors of emotional memory.

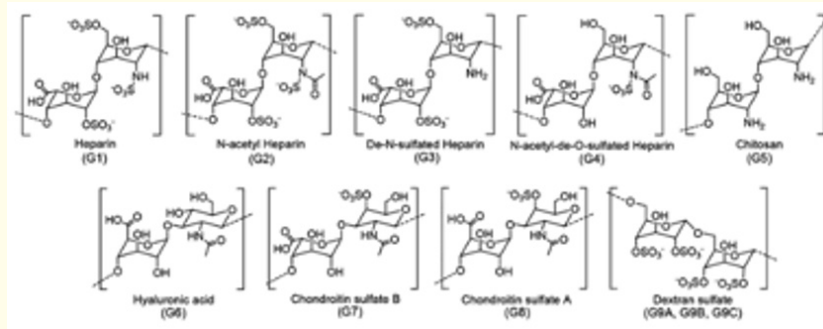


Figure 3: Representations of disaccharide units which polymerize into long chains. These polysaccharides do not react with the Golgi silver stain and thus remained invisible and unconsidered [37]. The stereo-topologies of polymerized sulfated dimers represent near infinite coding options.

Coding theory

One asks: What constitutes the processes “encode” or “store” in a physiologic being? DNA comes to mind but its processes are too slow to perform for “real time” memory or consciousness. Some [42,43]. Rather, the DNA system builds the systems that achieve psychic capabilities like memory and consciousness. Some cite Edelman and Damasio on dependence of consciousness on memory, but do not describe how such memory is rendered operational in the brain. They call on “information” but do not define the physicality of “information” [2]. Moreover, gap junctions and synaptic contacts do not rationalize the ability to encode emotive memory.

Regarding the coding options of the tripartite mechanism for encoding memory, it is much more complex than the binary bit system (0 1) where one could calculate the information of a message length L , as:

$$[\text{Info}] = 2^L$$

But this mathematical approach divorces [info] from “meaning”, as it is incapable of encoding the subjective import of stimuli. There is no binary calculus for emotions, “value” or “meaning”.

One could consider that the neural net generates a new mental state of psychic proportions, recalled as memory. The transformation of sensation to cognitive information (cog-info) with >80

NTs as coding effectors, where analogous to the above equation of [info], a sensate message could be formulated as:

$$[\text{Cog-info}] = 80^L$$

At this time, there is no accepted mathematical theory of [Cog-info] that permits encoding of an emotive message with 80 encoders. Moreover, the encoders are not identical, fear is not equivalent to hunger, “pain” is not equivalent to “love”. etc. Thus, the above equation is totally inappropriate.

A code without “recognition” is just noise. Some propose that the glial-astrocyte clusters in the brain transform sensation (cog-info) into memory [44-55]. The brain cells “read” and “recognize” the memory encoded within the nECM/PNN, from which they recall (recognize) meaning (Figure 4).

Roberson and Sweatt [42] describe how molecules as diverse as protein kinases, prions, and transcription factors can participate in what they call “mnemogenic reactions”. They postulate mnemogenic reactions occur at the synapse and in the nucleus. They suggest that a specific type of “mnemogenic”, or memory-forming, chemical reaction is the basis of the engram, the physical trace of memory (see Semon). They discuss “molecular turnover” as affecting long-term information storage in the brain. For mnemogenic

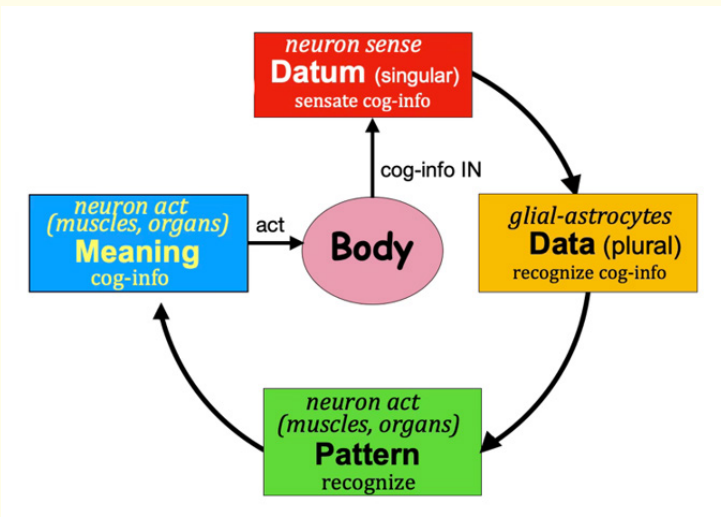


Figure 4: A “roadmap” of the transformation of sensory cog-info into a mental state that instigates a body reaction. Note that the body is central to all the process steps encircling (schematically) the brain. etc.) [50], and >80 NTs.

chemical reactions, Roberson and Sweatt [42] discuss the calcium/calmodulin-dependent protein kinase II (CaMKII) in a mnemogenic phosphorylation reaction. Other candidate reactions are autocatalytic glycosyltransferase or ADP-ribosyltransferase. Another option they propose are structural or conformational interactions. In the context of the mnemogenic reactions, they consider the pool of amino acid building blocks necessary to synthesize the bacteriophage λ repressor. As to locale, they suggest that the fundamental unit of information storage in the brain is the synapse.

Experimental

As to experimental results that buttress the tripartite mechanism, we point to our work with impedance electrodes coated with sulfated tetra-saccharide analogues of the nECM [39-41]. We demonstrated the selective but variable attachment of different elemental cations and neurotransmitters to such coated electrodes. This constituted an in vitro proof-of-concept test of the proposed tripartite mechanism i.e. the complexation of sulfated saccharides with metal cations and NTs.

Role of Astrocytes and the nECM/PNN in encoding memory

Astrocytes are increasingly recognized as dynamic regulators of memory formation and recall in the central nervous system. Beyond their classical support roles, astrocytes encode, retrieve, and integrate cognitive and emotive information by direct contact with neurons and dynamic interactions with the surrounding neural extracellular matrix/perineuronal net (nECM/PNN). This matrix, once invisible to early histological techniques, is now visualized as a structurally versatile and chemically specific polymeric network capable of molecular memory storage. Within the presented tripartite model, astrocyte clusters serve as the primary agents writing information into—and reading from—the nECM/PNN. Metal cations (such as Ca^{2+} , Mg^{2+} , Zn^{2+} , Cu^{2+} , Mn^{2+}) and a wide spectrum of neurotransmitters act as mobile chemical dopants that encode individual memory episodes at specific molecular “addresses” determined by the sulfation and geometric complexity of the nECM/PNN. The resulting memory trace or “engram” is a physical, retrievable state, available for recall by astrocyte clusters and, through network effects, integrated into conscious experience.

We concur that astrocytes are the brain cells that decode the sensory information encoded in the nECM/PNN (memories) and transcend it into consciousness. Recent experiments describe the critical role of astrocyte ensembles in generating memory recall [44-55] as summarized below:

- Neurons - synaptic neural circuit conducts 2-way signal perceives sensations (cog-info) from distal senses and transmits them (electro-dynamically) to the brain. They “write” the cog-info into the nECM/PNN as memory (with metals and NTs; see tripartite mechanism).
- Astrocytes “read” the nECM/PNN (chemographically) and integrate this input as recall.
- “Recognition” is the hallmark of memory and the basis of consciousness.
- Mentation (conscious thought) is performed by clusters of brain astrocytes.
- Action required after mentation is chemodynamically signaled by astrocytes to the neural circuit, to electrodynamically instigate muscles and organs.

In short, the astrocytes do the remembering and thinking, the neurons are involved in sensing and activating muscles and glands (Equ. 2). Recent experiments describe the critical role of astrocyte ensembles in generating memory recall [55].

Of course, the neurons and glial cells (astrocytes) are intimately linked, so that any drug or event that decreases the optimal performance of one would negatively impact on the performance of the other. Experimentally or behaviorally, it would be difficult to distinguish.

Anatomical studies show that human astrocytes form innumerable clusters that integrate cognitive information (cog-info) to achieve consciousness. These cells are crucial for cognitive functions, including learning and explicit memories. Evidence indicates that glia, particularly astrocytes, are involved in all facets of cognitive processes. Clearly, without describing the process of mentation in molecular terms, we will not grasp its essence. We begin by identifying the coding effectors, namely >5 metal cations (Zn^{+2} , Ca^{+2} , Mg^{+2} , Cu^{+2} , Mn^{+2} , etc.) [50], and >80 NTs.

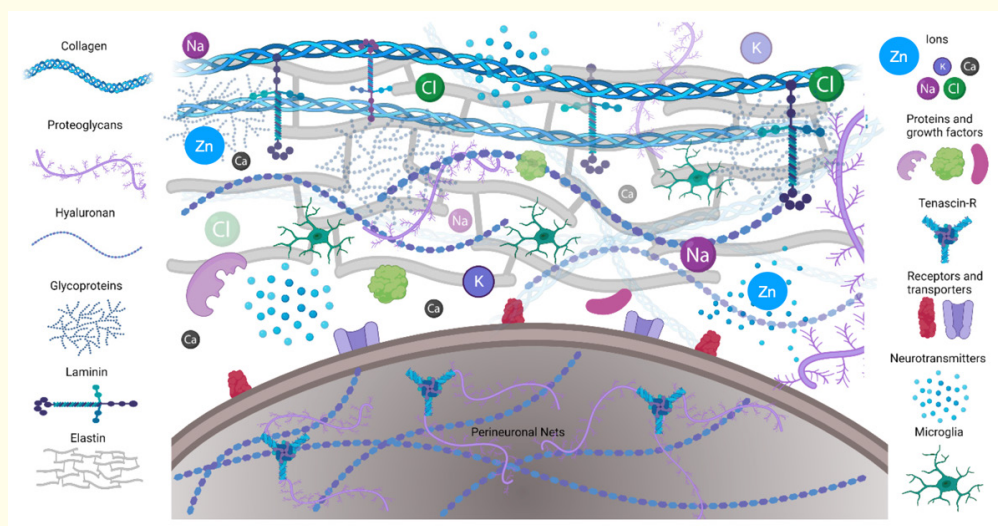


Figure 5: Cartoon of nECM/PNN matrix which engulfs all brain cells (adopted from 57).

The sulfation patterns of the GAGs determine binding of metal cations and NTs (dopants). For example, chondroitin sulfate glycosaminoglycans (CS-GAGs) are repeating disaccharide glycan units (CS-GAGs) as repeating disaccharides that bind to the core proteoglycan proteins. The sulfation patterns of the GAGs determine binding to metal cations and NTs.

Neurobiological significance

This model offers a unifying, material basis for memory and mentation that moves beyond historically exclusive focus on synaptic signaling or binary computation. It positions the nECM/PNN as a molecular substrate for persistent information storage,

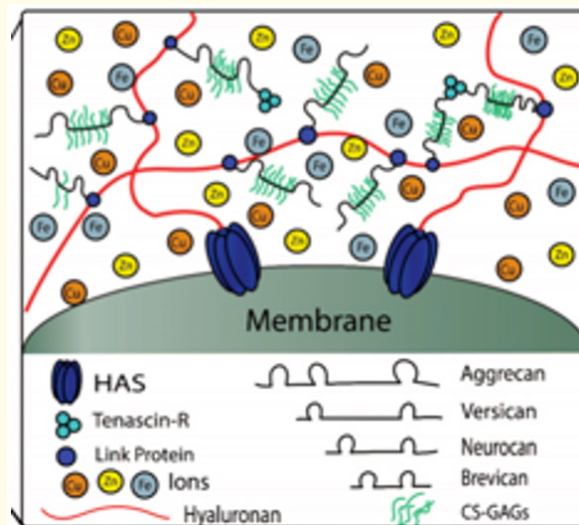


Figure 5B: Cartoon of metal cations interacting with components of the nECM/PNN depicted as: Chondroitin sulfate proteoglycans (CS-GAGs), such as aggrecan, versican, neurocan, and brevican, all connected to the hyaluronan backbone (adapted from 58).

and astrocytes as essential decoders—bridging sensory input and behavioral output with flexible, context-aware cognition and emotion. Recent research demonstrates that disrupting astrocyte-neuron or astrocyte-matrix interactions leads to deficits in memory, learning, and mood regulation. This underscores the essential role of astrocyte clusters and their nECM/PNN environments in supporting adaptive behavior and cognitive health.

Clinical correlations

Because the model makes specific predictions about how memory is formed, strengthened, or lost at the molecular level, it supports innovative strategies for addressing disorders of memory, learning, and mood. For example, manipulating astrocytic function or targeting the chemical composition of the nECM/PNN could provide novel therapeutic pathways for treating depression, PTSD, and cognitive decline.

More clinical evidence augments the credibility of the tripartite mechanism. The processes for decayed functioning of the neural net resulting in Alzheimer memory loss include either inhibition of the biosynthesis of nECM or its degradation (as by redox (Fenton) or enzymatic reactions). There are other decay pathways resulting in the loss of memory function, correspond to uncontrolled lipid

peroxidation (i.e. endocannabinoids) or autoimmune reactions. The latter correlates with the presence of antibodies to metallothionein in Alzheimer and autism patients. Interference with the optimal operation of the tripartite mechanism is reflected by clinical features of forgetting in patients with degenerative disorders [4-7,65-69].

Educational and cognitive science applications

The framework may inform new biological theories of learning and teaching, suggesting that educational interventions could one day target astrocyte signaling or nECM/PNN plasticity to enhance memory stability, retrieval, and creative thinking. It suggests that the physical “addresses” in the nECM/PNN, modulated by emotional, attentional, and neuromodulatory states, form the biochemical basis of lasting, adaptive knowledge. Comparative studies across species and human clinical populations will be critical in refining the tripartite model and revealing fundamental coding principles of learning, memory, and emotion.

Model limitations and future directions

There are many gaps in our comprehension. We lack a theory of how >5 metals and >100 NTs can encode memory, as compared

to the binary (0 1) Info Theory. Thus, we have no Cog-Info Theory ($n_m > 5$, $n_{NT} > 100$) analogous to computer binary code ($n = 2$) theory. It is not clear how phase transitions from physical and chemical states to subjective experience ("mentation") occur at the molecular or systems level.

Further experimental validation is needed, particularly regarding the real-time biochemical dynamics of nECM/PNN encoding and astrocyte cluster decision-making during memory recall and behavior. We are still cataloguing all the various cell types that participate in brain function [71]. For example, there are words that we wish to use but are inappropriate, such as "transform" and "dimension".... we prefer "transcend" and "realm"

respectively. Mental processes do not involve physical modifications of brain anatomy or visible space. Thus, there are many details that require clarification regarding the mechanism of our mentality. At best, it occurs at the level of molecular interactions. Detailed description will require a paradigm shift in the definitions of force and field (List 1).

At this point, we have identified the major components of the mentation process and suggest a memory mechanism in a manner consonant with our biochemical understanding of the workings of our whole body. We present a schema (Figure 6) of the brain processing but await further elucidation and inspiration to better comprehend the workings of our mind.

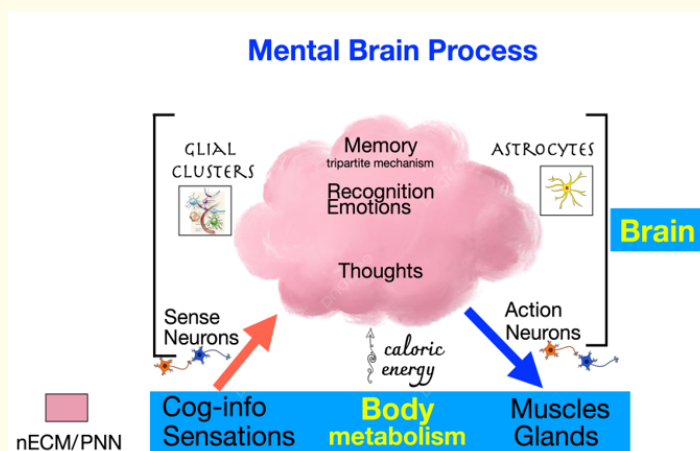


Figure 6: A conceptual schema of the brain's cellular components and biochemical processes that are invoked to generate mental states. The continuing review of tripartite memory encoded within the nECM/PNN (56-62) by glial astrocyte clusters (is fueled by caloric energy.

Conclusions

The tripartite model of memory and mentation provides a fresh, biochemically explicit account of how the brain encodes, stores, and retrieves cognitive and affective information at the molecular level. By recognizing the central roles of astrocyte clusters and the nECM/PNN, and by positing memory as a physical, storable molecular state, the theory bridges neuroscience, chemistry, and subjective experience. This integrated approach encourages renewed investigation of mental phenomena, implications for education and mental health, and the molecular machinery underlying consciousness.

The neuron-body circuit is tasked with sensing the environment (cognitive information, cog-info). It communicates sensation signals (feelings) to the brain. These signals are received by special anatomical regions of the brain (particularly clusters of glial cells in the amygdala, insula, and prefrontal cortex) to process and evaluate the emotive quality and meaning of sensory input [44-56].

Neuron-glial (astrocyte) networks are the multi-lane signal highway of the brain. Employing chem-electric encoding into the nECM/PNN (i.e. the memory library, see tripartite mechanism, [28-

35]), the cell circuit recalls previously encoded memory of experience to generate mentality. While most attention has focused on signaling and connectivity of neurons, the many astrocytes associated with the neurons play critical roles [33-56], as for example:

- Astrocytes regulate emotional processes and mood states. Clinically in humans, they have been shown to influence mood disorders (e.g., depression, anxiety).
- Astrocytes help regulate emotional arousal by amplifying neuromodulatory signals and triggering state transitions in the brain during high arousal or emotional events.

Thus, we contemplate a schema of brain mentation where the body sends neuronal signals (cog-info) to the brain, where it is processed by the astrocyte/glial clusters which transcend cog-info into memory and mentality. Note that the astrocytes are intimately connected to the neurons and also enmeshed with the nECM/PNN. The clusters of astrocytes [44-56] in the amygdala and other brain anatomic regions “read” and decode the emotive cog-info encoded in the nECM/PNN (see tripartite mechanism of memory), achieving conscious mentation to determine appropriate body reactions via body-directed neuronal circuits, as schematically illustrated in Figure 6 which considers the following mentation components:

- Neurons sense environment and signal the glial cells in the brain
- Glial cell complex converts (“write”) sensate signals into the nECM/PNN [58] (i.e. tripartite memory code).
- The glial complex constantly reviews the nECM/PNN code library i.e. mentation.
- The glial complex’s decisions to act are transmitted to the neural circuit.
- The neural circuit activates appropriate muscles, organs and glands.

We have read many papers that deal with memory and consciousness, notably to memory loss in Alzheimer disorder [67-70]. At this stage, our scoring of a paper’s relevance relates to its inclusion of a biochemical twist to its presentation. Just as in any medical discussion of the workings of a body organ (i.e. spleen, liver, lungs, blood, etc.), we require a biochemically-based mechanism

that invokes all the components that participate in the brain’s generation of mentality. Here, we enumerate the key classes of components that enable the encoding of memory, namely: cells (neurons, glial, astrocytes), the nECM encasing all cells and dopants (metals, NTs), a tripartite mechanism.

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Authorship

The authors share equal responsibility for the concepts expressed and the writing of this manuscript.

Conflict of Interest

This work received no external funding.

GM is a founder of MX Biotech Ltd., involved in developing biotechnologies.

CG is an Active Emeritus Professor of Chemistry at the Hebrew University of Jerusalem, involved in developing protein and peptide-based drugs.

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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