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The Molecular Basis of Memory: Remembering and Forgetting

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ABSTRACT

What lies between the vital physiology and pathology of cognitive aging?

To comprehend the brain's mental function and dysfunction, we focus on memory, its formation and loss. Our expanded tripartite mechanism of memory involves the following compartments: Stimulated brain cells (neurons + glial cells) which secrete dopants (>10 metals and >80 neuro-transmitters (NTs) and glio-transmitters (GTs)) into the extracellular matrix (nECM/PNN) enveloping all brain cells, that performs as a "memory material". The metal-centered complexes formed within the nECM/PNN are molecular correlates of cognitive units of information (cuinfo) that encode experience. The transmitters (NTs+GTs) embody emotive quality that elicit physiologic reactions from organs and glands to encode emotive states. As for decoding the cuinfo, aggregates (mosaics) of sensors (GPCR- and K-channel family proteins) within the lipid-bilayer comprising the cell membranes are capable of "reading" and integrating the cuinfo, transliterating them into an experiential mental state.

As to memory loss, aside from gross injuries or anatomical abnormalities, we look to molecular-level decay, which involve processes such as Toxicity or deficiency of trace metals, degradation of the nECM/PNN or it's by enzymatic or redox (Fenton) reactions, uncontrolled lipid peroxidation (i.e. endocannabinoids) or autoimmune antibodies (i.e. anti- metallothionein) or lysozyme amyloid fibril formation. Interference with the optimal operation of the expanded tripartite mechanism of emotive memory is reflected by clinical features of memory loss in patients with degenerative disorders.

Keywords

Neuron, Glia, Extracellular matrix, Metals, Biomodulators, Emotions, Alzheimer, Degradation.

Abbreviations

Info: Information, cog-info: Cognitive Information, *cuinfo*:- Cognitive unit(s) of Information, nECM/PNN: Neural Extracellular Catrix/ Perineural Net, AD & PD: Alzheimer and Parkinsons diseases respectively.

Background

"Time's the thief of memory."
— Stephen King, The Gunslinger

"Nothing is ever really lost to us, as long as we remember it."
— L.M. Montgomery, The Story Girl

"Memory is a part of the present. It builds us up inside; it knits our bones to our muscles and keeps our hearts pumping. It is memory that reminds our bodies to work, and memory that reminds our spirits to work: it keeps us who we are."
— Gregory Maguire, Son of a Witch

"Death leaves a heartache no one can heal,
Love leaves a memory no one can steal".
(From an Irish headstone)
— Richard Puz, The Carolinian

"*You shall blot out the memory of Amalek from under heaven*."
• Deuteronomy. 25:19.

There is a profound connection between the physiology of the body and the psychology of the neural net. To adopt a phrase from quantum mechanics, they are "entangled". However, the mechanism of the brain's unique mental talents (cognition, thought, and language) which involve memories and their loss remains opaque. We are in the dark, regarding the functional link between molecular physiology and mentality. This has been the perpetual enigma for philosophers and cognitive scientists [1-4], particularly acute for clinicians treating patients with memory deficits.

For example, some of the earliest symptoms of degenerative disorders such as Alzheimer disorder (AD) and Parkinson disorder (PD) are manifest as memory loss. Much has been published in the neurological literature about brain activity, particularly with the advent of non-invasive techniques (fMRI, CT scan, PET) [5-14]. However, we still lack a molecular-scaled organizing principle to describe the neural talent of recalling experience.

Evidence has linked memory disorders to a variety of primary causes such an unusual disposition of trace metals in the brain (notably toxicity or deficiency of trace metals i.e. Al, Cu, Fe, Mn, Zn), oxidative stress, immune reactions, lipid peroxidation and the release of β-amyloid peptides cleaved from precursor proteins associated with cellular tubulin, correlating with the onset of AD [15-20].

As with all aspects of normal animal development after birth, an optimal state is achieved with maturation, and then eventually decays. For humans, one expects memory to achieve peak performance upon maturity (~16-25 yrs), followed by gradual decay with age. There may be an accelerated rate of decay corresponding to a rapid loss of mental function, termed "dementia". At some point during the aging of the neural creature (after mild cognitive impairment, MCI), a more rapid degradative process (Alz point) can begin to overwhelm the normal slow decay of the mental functioning, manifest as acute, irreversible loss of memory, as schematically represented in Figure 1.

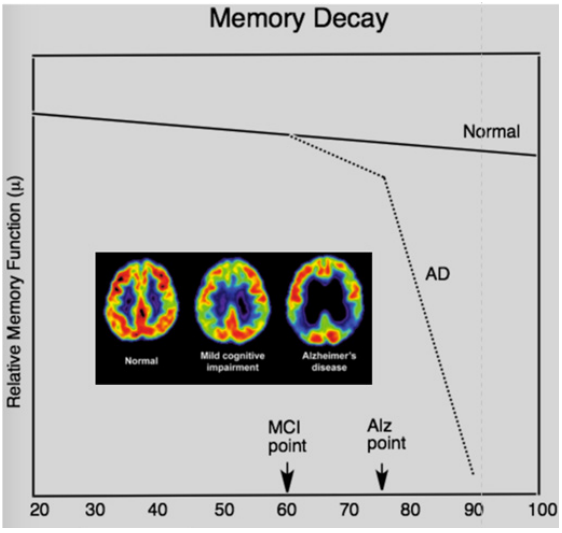


Figure 1: Hypothesized kinetics of memory loss in a normal ageing human and one with Alzheimer disorder (AD). The inset shows a set of fMRI scans of patient brains with mild cognitive impairment (MCI), followed by obvious reduction of brain tissue (Alz point) including loss of nECM (adapted from 14).

However, to understand what went wrong, one needs to understand how the brain system functions under optimal conditions. Like all other body organs, one could consider that the memory function achieved by brain cell signaling must be based on known metabolic processes with available molecular components. At this stage of our evaluation, we avoid dealing with the memory of humans, as it involves language, itself a complex memory system. Rather, we wish to consider the universal memory/forgetting mechanism of non-verbal neural creatures.

A recent review considered the processes underlying the phenomenon of forgetting [21]. Presuming a forgetting mechanism based on synaptic contacts and molecular interactions, the review focused on problematic cell-cell interactions as itemized below:
Extinction – Inhibition of conditioned response to stimulus by unassociated stimulus.

Interference – of one memory trace by another, new memory impairing the recall of old memory.

Neurogenesis – newly formed neurons integrated into the network disrupt pre-existing connections.

Aging - decay of the brain cell signaling system.

Cell Death - Specific brain cells encoding specific memory traces die.

De-potentiation - Facilitated by β-amyloid peptide (Aβ) interference with NMDAR receptors, leading to memory decay.

Certain cell receptors and neurotransmitters were implicated in memory loss, namely:
AMPARs - Glutamtergic receptors; conductance of AMPARs present in synapse.

NMDA Receptors - Operating pores that permit the flow of Ca+2, Na+, K+

Enzymes - Phosphatases (PP1, PP2A, CaMKIIa, PKM, MAPK, and kinases that affect Phosphorylation reactions.

Neuromodulators - Dopamine and other modulators.

Though presented as a molecular process, the above review [21] was essentially a description of cell signaling processes. We opine that one needs to consider a more detailed molecular mechanism for memory, to explain both its recall and its loss.

Forgetting

In our view, mechanism of remembering and forgetting are Janus-processes (Figure 2), one being the converse/inverse of the other.

Figure 2: A drawing of the two-faced Roman god, Janus (Wikipedia).

To satisfy our need for a molecular basis for remembering linked to forgetting, we pursue an expanded version of our tripartite mechanism, as detailed below.

Expanded Tripartite Mechanism of Memory

In earlier parts of this series, we proposed a tripartite mechanism of memory, which involved the dynamic interactions of 3 physiologic compartments [22-27]. Here, we present an expanded version of this mechanism, as follows:

• Brain cells, notably neurons (highly extended cells that form long-distant circuits to muscles and glands via synaptic contacts) and glial cells, which surround neurons and their synaptic regions [28-32]. When stimulated, each cell type ejects biomodulating molecules (see dopants).

• Extracellular matrix with perineural net (nECM/PNN) - the anionic matrix encapsulating the brain cells. It is a polymeric hydrogel of hyaluronates incorporating lattices of chondroitin/heparan sulfates, which all embed the neurons and glial cells. The nECM/PNN functions as a "memory material" analogous to the matrix in computer memory chips [33-47].

• Dopants – metal cations, neurotransmitters (NTs) and glio-transmitters (GTs) [48-54] ejected by brain cells into the nECM/PNN, which serve as biomodulators which elicit physiologic responses and encode emotive cognitive information.

A general characteristic of a "memory material" used for memory chips is "its ability to store the (information) "state" of a system at a given time, and access such information, or part of it, at some later time. This "state" could be the spin polarization, or the doping profile, or some other physical characteristic of the system" [33].

For neural memory, the nECM/PNN around neural cells is the "memory material" which is doped with physiologically available metal cations and transmitter molecules (NTs/GTs) ejected by neurons and glial cells. Our tripartite mechanism provides a psychochemical rationale for encoding the neural memory system. The nECM performs as the 'medium of representation'; the dopants (metals and NTs) are the 'symbols of representation' [55].

Specifically, metal-centered complexes are formed by the binding of ejected dopants (metal cations and NTs/GTs at electron-rich moieties (addresses) in the nECM/PNN enveloping the cells. Such NT/GT complexes are chemically more stable and more impervious to degradation reactions than proteins, thereby more available for recall [53]. Such complexes embody cognitive units of information (*cuinfo*) chemo-graphically represented below (Figure 3). They represent the "engram", the physicality of the memory trace first proposed by Semon [56,57].

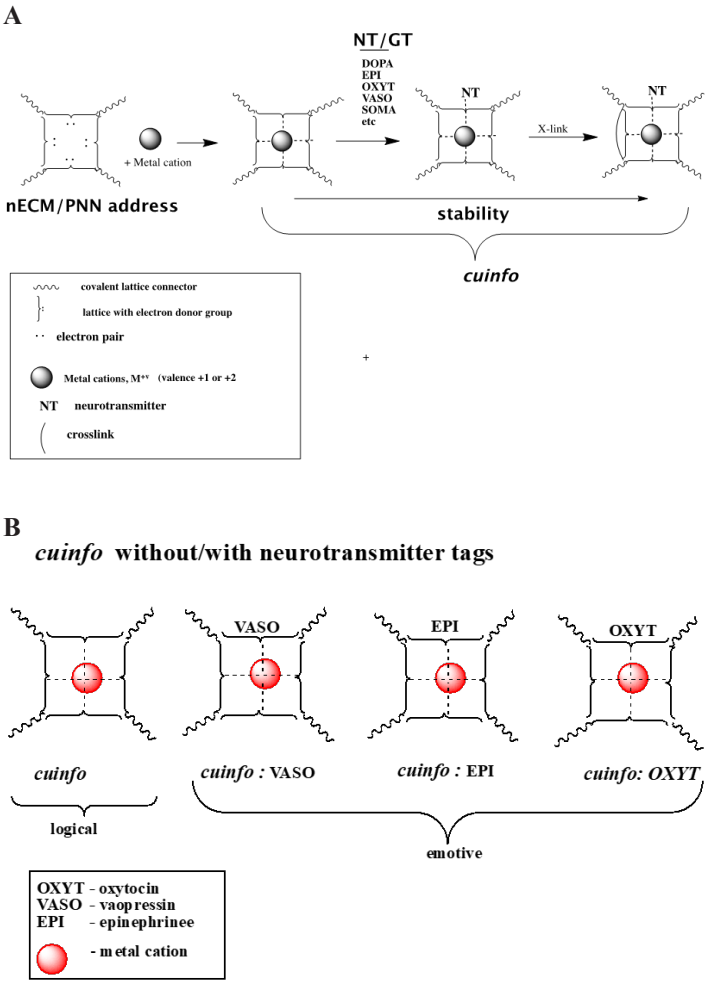


Figure 3 A,B: Chemographic representations provides a chemographic shorthand for considering the nECM/PNN addresses and the chemical types of *cuinfo* that can be formed through metal binding and complexation with neuro-glio-transmitters (NTs/GTs) which are the molecular conveyors (elicitors and encoders) of emotions.

We previously employed the term "neuron" to indicate all cells within the brain, but here specifically include glia (astrocytes), which outnumber the neuron by factors of up to 10, depending on the anatomic compartment. We consider that all these cells,

which are in synaptic as well as non-synaptic contact with one another through the nECM/PNN operate as a "cloud" of cognitive information which permits of mentation based on memory. The metal-centered complexes are molecular correlates of cognitive units of information (*cuinfo*). The neurons and glial cells eject the contents of vesicles with metals and NTs/GTs to encode (i.e. "write") cognitive information, Thus, memory is quantized, encoded and stored outside the brain cells, in their extracellular environment. We here and previous publications for detailed background and supportive evidence cited many publications.

The cells operate in "read" mode to decode and process the *cuinfo* stored within the nECM/PNN (Figure 4) with the millions of receptor-sensors (i.e. integrins, GPCR assemblies, K-channels and Acetylcholine receptors) expressed on their surface [24], which perform as "biologic micro-processors".

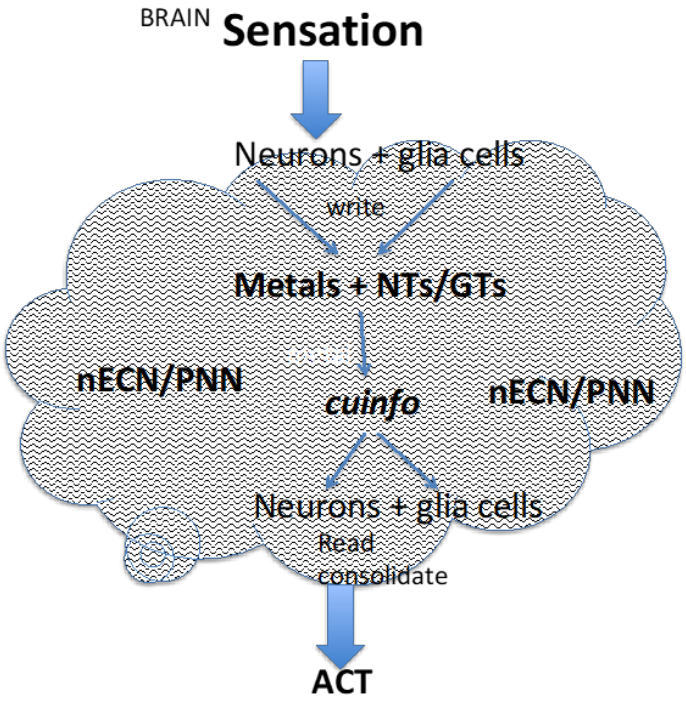


Figure 4: Schematic representation of the tripartite mechanism, of emotive memory units (*cuinfo*) defined as the combination of nECM/PNN + dopants, surrounding the neuron. The receptors diffuse over the cell surfaces and are exposed to many addresses of the external nECM/PNN.

Discussion

The mystery of memory cannot be revealed unless it is reduced from philosophic speculation [1-4] to biochemical understanding. In keeping with other explanations of biologic processes, we have chosen the language and iconography of chemistry to comprehend the function called emotive memory, as discussed in detail in our previous reports [22-27]. Here, we wish to apply the lessons of the expanded tripartite mechanism, applied to the loss of memory experienced by individuals suffering from Alzheimer disorders (AD) or Parkinson disorder (PD).

The pathological features of AD/PD include:

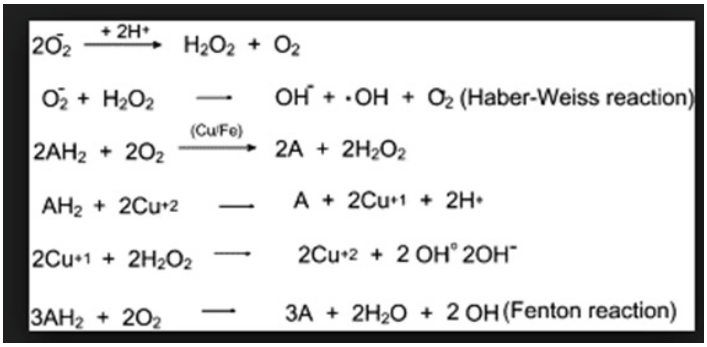
- Protein degradation – amyloid peptide release and precipitation
- Lipid oxidation - excess circulating lipids
- Trace metal (Cu Fe Zn) - precipitation and mal-distribution
- Low metallothionein levels – autoimmune effects, poor metal transport.
- Poor insulin metabolism.

Q: *Assuming that our above-described expanded tripartite mechanism is operative, how does it explain the clinical findings associated with such neuro-degenerative conditions?*

A number of considerations are possible, as listed below:

Redox Reactions

Multivalent metals that participate in the encoding of metal complexes within the nECM that encode memory as *cuinfo*, notably Cu and Fe, could participate in ascorbate-instigated, metal-catalyzed, Haber-Weiss (Fenton) redox reactions [57-60] to release the deleterious OH radicals (Figure 5).



These redox reactions can instigate a number of effects including:

- Protein oxidation degradation and chain breaks resulting in release of amyloid peptides (which are toxic in their own right),
- Lipid oxidation,
- Condensation reactions,
- Release of trace metal cations due to modification of anionic binding moieties of the nECM.

The loss of memory by Alzheimer patients is an acute symptom of such a neuro-degenerative redox degradation of the nECM. It is associated with amyloid peptide release/toxicity as well as unbalanced metal (Al, Cu, Fe, Zn) metabolism [60-65]. Unlike enzymatic reactions, which are specific for one or another substrate (like a rifle), whereas the redox reactions can effectively destroy the entire locale in which they are generated (like a shotgun). Experimental examples of Fenton reactions were described for albumin and fibrinogen [65-70].

Oxidative cycling of multivalent metals via Fenton reactions with reductants, such as vit C or glutathione, which diffuse through the nECM to be absorbed by the cells (Figure 6). The tethered metals generate reactive OH' radicals, which can degrade local components of the cells as well as the nECM/PNN. Within the cell, uncontrolled release of ascorbate and glutathione react with

amyloid precursor protein from cytoplasmic tubulin, releases amyloid peptides. The resultant altered shape of the cells corresponds to change in the local nECM.

Lipids that comprise cell membranes are also derivatized due to such redox reactions. Ancillary to these effects is the precipitation of metals, which no longer serve as dopants within the now-degraded nECM/PNN. The combined effects of such chemical degradation reactions is reflected by the composite loss of memory function.

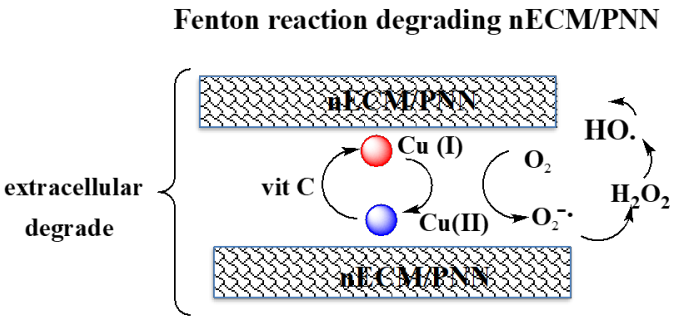


Figure 6: Schematic of the redox cycling of multivalent copper tethered to nECM/PNN, serving as a center for the generation of the OH. radical (Fenton Reaction), which can degrade the nECM/PNN and whatever proteins are nearby, such as amyloid precursor protein.

Degradative Enzymes

Enzymes permeating the matrix, including metallo-peptidases, can also degrade the nECM/PNN. Activation of such enzymes could cascade into significant degradation of the polymeric lattice, with resultant loss of memory units (*cuinfo*) resulting in forgetting.

Decreased Membrane Fluidity

Mobile cell sensors (i.e. GPCR receptors), that are intercalated within the neural/glial membranes and diffuse therein [71,72], are responsible for the "read" function of brain cells. However, if the membrane fluidity were decreased, such as by incorporating hydrophilic blockers, such as endo-cannabanoids, this too would result in memory loss.

Endo-cannabinoids (Endocan)

Endocans are a type of neurotransmitters that are released by vesicles from the post-synaptic neuron into the synapse activating cannabinoid receptors in the postsynaptic neurons. The chemical makeup is very different from the other NTs, comprising a C-20 hydrocabon domain (arachadonic acid derivative with variously placed double bonds) and a metal-chelating terminus [73,74] (Figure 7). Thus, Endocans can form ternary complex with *cuinfo* in the nECM and be inserted into the membrane via their hydrophobic tail. This could alter the fluidity of the membrane lipid bilayer and the ability of the mobile sensors to access the nECM.

The "read/write" mechanisms of brain cell processing of cog-info based on our expanded interpretation of the tripartite mechanism. In the normal nervous system, Endocans are released in the synapse and activate receptors to perform their normal functions. However, malfunction in the endo Endocan system cause excess release of Endocan both in the periphery and the central nervous system. This excess Endocan reaches the neural membrane in the memory regions of the brain (e.g. hippocampus) that are involved in memory "reading". As the Endocans are bivalent regarding their chemical affinities, they can either bind to metals in *cuinfo* or insert into the lipid bilayer of the membrane, causing loss of fluidity in GPCR movement essential for memory reading (Figure 8).

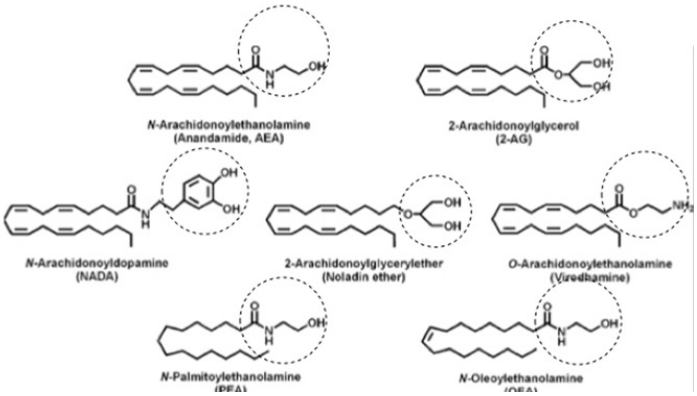


Figure 7: Endocannabinoids (Endocan) structures with metal-binding regions outlined in dotted areas [70,71].

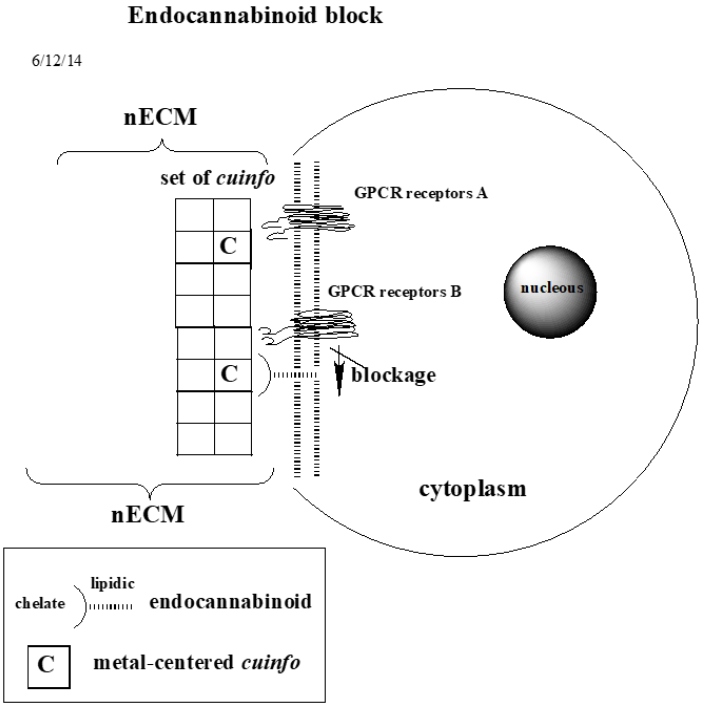


Figure 8: Schematic diagram of how endocannabinoids (Endocans) inserted within the lipid bilayer, block membrane diffusion of GPCR receptors of neurons, thereby decreasing memory function.

In the normal nervous system, Endocans are released in the synapse and activate CBD receptors to perform their normal functions. However, malfunction in the endocanabinoid system cause excess release of Endocans both in the peripheral and the central nervous system. This excess EC reaches the membrane regions of the brain cells that are involved in "reading" memory units.

Endocans are unique and different from other fats in the sense that they can bind to both the metal in the *cuinfo* and be inserted into the adjacent membrane. Even without G-coupled protein receptors, one could consider that the Endocans could become inserted directly into the lipid bilayer of the cell membrane by hydrophobic affinity. For example, it is known that arachadonic acid binds to platelet membranes and is involved in the transformation of round, lentilic discs into multi-villi "cells" that attach to one another to instigate the blood coagulation cascade and form a platelet plug to stop bleeding. Thus, arachanoids can interact directly with lipid bilayers, somehow instigating shape change and synaptic plasticity in platelets and neurons respectively.

In addition, insertion of an Endocan molecule into the bilayer could inhibit the movement of the GPCR receptors, resulting in the inability to "read" the *cuinfo* encoded around the brain cells. In that in pathological cases excess EC could bound to a specific nECM address via its chelating head and stuck into the membrane around the GPCR ensemble in the adjacent membrane, slowing-down or stopping the lateral movement of the GPCR ensemble [75,76], thereby preventing the reading of the *cuinfo* relevant to a particular memory…hence forgetting.

Metallothionein (MT) Problems

Histologic and other studies indicate that the MTs (with their load of cations) perform essential transport function of metals to reach the nECM/PNN, and permeate it to attach to the cell's surface membrane. Overall, the MT can absorb and transport cations through the intestines into the blood, and permeate the blood-brain barrier, to reach the ECM/PNN and brain cells. One can also note that occasionally, antibodies to MT coincide with the onset of MT-related memory disfunctions [77-82].

Insulin Metabolism

Insulin modulates vasoreactivity, lipid metabolism, and inflammation. It also has a role in proteostasis, influencing clearance of the amyloid β peptide and phosphorylation of tau. Insulin resistance is a pathological condition in which cells fail to respond to the peptide insulin as observed in Alzheimer's disease. Studies also depict a correlation with other neurodegenerative conditions (i.e. Parkinson's disease and Huntington's disease) [83-86].

Amyloid Formation

The loss of memory by Alzheimer patients is an early symptom of their neuro-degenerative state. It is associated with amyloid peptide release/toxicity as well as unbalanced metal (Al, Cu, Fe, Zn) distribution and metabolism.

Autophagy is the principal pathway for lysosomal degradation of obsolete proteins and organelles, associated with the formation of plaques. Imaging and histochemical techniques established that neurons are the origin of the vast majority of senile plaques in AD mouse models [87,88].

Vaso-circulation

K+ channel-mediated vasodilation could account for the clinical cerebrovascular presentation seen in AD patients [87]. Vasodilation in response to direct pharmacological activation of endothelial SK/IK channels was also reduced in AS model mice with reduced blood flow and crippled functional hyperemia.

Clinical Aspects

The brain's "mentation circuit" comprises a complex of connected (associated, aggregated) receptors/sensor, described as mosaics/rafts, which perform a function unique to brain cell networks, characterized by "hub criteria" (connectivity & nodes), and clustering coefficient. Its malfunctioning has been implicated in multiple neurological disorders. Assuming an optimal performance of a human to be at age 18 years, one can schematize the gradual loss of mental function by a cascade of events. The relative memory function) could be quantified by virtue of a standard memory test performed by the individual at different ages or compared to an average. The optimum in humans is assumed to be at 18-22 years, with initial rate of decay being slow and imperceptible. However, at the "Alz" time point, a sudden decrease in function occurs possibly associated with a specific triggering process. Below, we describe some of the triggering events might be and discuss how to address them.

However, how do the effects all relate to the normal brain memory process and its decay with age? A graphic summary of the many pathways by which memory loss could be associated with specific decay processes is presented in Figure 9.

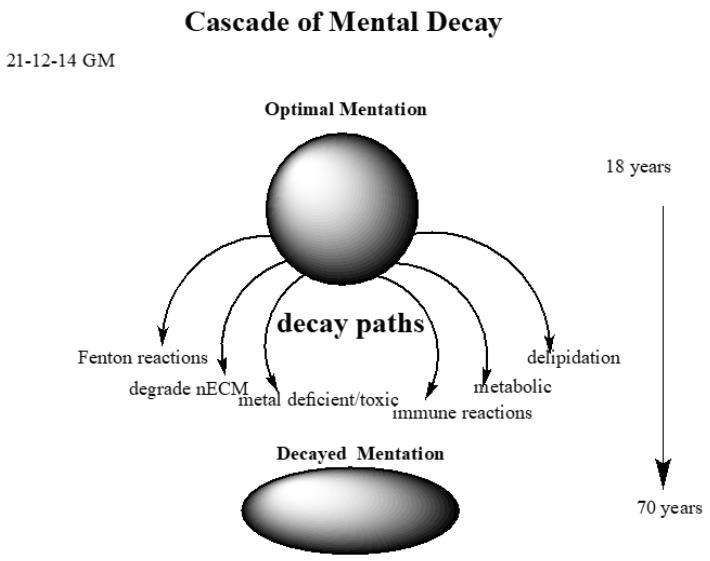


Figure 9: Schematic representation of pathways whereby mentation could decay with time, manifest as memory loss.

We interpret the decay of neural memory in the context of the tripartite mechanism, as a confirmation that metals play a central role in encoding /storing cog-info within the nECM. Oxidative cycling of multivalent metals via a site-specific Fenton reaction with reducing agents, such as vit C or glutathione, which diffuse through the brain. Their reaction with the tethered metals generates reactive OH. Radicals, which can degrade local components of the nECM as well as amyloid precursor protein, releasing amyloid peptides.

Conclusion

The scientific enterprise is fueled by a hunger to understand the nature of things…for knowledge of matter, motion and mind. We know much about the vast cosmos and sub-atomic, quantum reality, but have huge gaps in our knowledge of how brain cells experience psychic effects such as emotive memory and the loss of such.

Rather, one must be aware that like a "Russian doll", the workings of the brain are nested, operating at various scales, ranging from anatomic compartments, to complex neural networks. For the purposes of these discussions, we often employ the term "neuron" to include helper cells (astrocytes, glia). In any case, the localities around the cells (i.e. nECM/PNN) must be described in atomic or molecular detail to comprehend the process of emotive memory.

Obviously, mentation does not occur on the level of the single neuron, but on a collection (ensemble, network, circuit) of billions of interconnecting neurons surrounded by glial cells, which together perform in an orchestrated manner- each cell contributing to the mentation process.

An explanation of how the brain generates memory requires not only an understanding of how it is anatomically organized in molecular detail but how it breaks down. Histologic conception of the brain cells must include reference to the environment in which the cells are cocooned.

During the past decade, three main hypotheses on the pathogenesis of AD have emerged that focus on different features of the disease:

- The amyloid cascade hypothesis.
- The metal ion hypothesis.
- The oxidative stress/insulin hypothesis.

The expanded tripartite mechanism permits us to consider these as different facets of a common process, as discussed above.

To slow down the decay of mental function, a number of lifestyle parameters have been suggested by diverse cultural models (Zen, Yoga, Chinese, vegan, Jewish, psychoanalytic re: Jung, Reich) [90-95], listed below.

Pillars to a Healthy Lifestyle

- Regular exercise
- Healthy diet (low fat, low sugar, low alcohol: adequate mineral intake, gluten/casein free diet)/fasting
- Quality sleep
- Stress management
- Active social life
- Intellectual stimulation
- Good sex
- Perform acts of kindness

We are all destined to metabolically decay and die (the ultimate form of forgetting) but we want to slow this down as much as possible. The behavioral guidelines reflect an intuited connection between physiology and psychology.

The material basis for neural memory has been the goal of neuroscientists from the time of Golgi and Cajal. The above-expanded tripartite mechanism permits one to consider memory loss such as in AD and other neurodegenerative diseases, in the context of dysfunctions of metal metabolism or the degradation of the nECM around brain cells.

I hope that some heuristic direction or clinical approaches to memory disorders might arise from the above biochemical description of emotive memory.

Acknowledgement

(By GM). Dedicated to my wife, my muse and collaborator, the artist Georgette Batlle (1940-2009), who never forgot a birthday. 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.

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