

The Molecular Basis of Neural Memory. Part 6: Chemical Coding of Logical and Emotive Modes

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ABSTRACT

Neural memory of man, with many aspects (associative, cognitive, declarative, episodic, implicit, procedural, semantic, working, short/long-term, etc), emerges from the mental processes of the active neural net. We focus on what happens at the cellular-molecular interphase. Our goal is to describe neural memory as a talent which evolved from simpler bacterial emotive signaling, all employing identical signaling molecules (biomodulators). We invoke a tripartite mechanism based on the interactions of 3 compartment which instigate “emotive memory”, but constrained by the laws of chemistry and capabilities of cell biology: [neurons] including helper cells (glia astrocytes); [nECM] (neural extracellular matrix); [dopants] (comprising diffusible metals and neurotransmitters (NTs). The nECM functions as a “memory material” which entangles the cells. The neuron ejects dopants from vesicles, to form metal-centered complexes, to encode cognitive units of information (cuinfo) (singular/plural) in the nECM, as chemographically represented. “Emotions” are “recalled feelings”. Psychic states (emotions) as well as physiologic responses (feelings), both are encoded with biomodulators which can bind to metals tethered to nECM, literally embodying “emotional memory”. The evolution of a brain operating in emotive and logical modes of memory, suggests a “phase” diagram. It starts with the (emotive) signaling of feelings with biomodulator molecules. Logic emerges as a new talent, coincident with the evolution of skull size, brain capacity, neural signaling modalities and molecular complexity. The tripartite mechanism permits of a chemical perspective to the evolution of “logical” and “emotive” modes of neural memory.

Key words: Cuinfo; Emotion; Mentation; Neurotransmitter; Metal complex

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BACKGROUND

“Every man’s memory is his private literature.”-Aldous Huxley.

“I can only note that the past is beautiful because one never realises an emotion at the time. It expands later, and thus we don’t have complete emotions about the present, only about the past.”-Virginia Woolf.

Though pondered for millennia, neural mentation (cognition/thought), memory and emotions experienced by all creatures, remain puzzling, psychic phenomena, examined by philosophers as well as physicists^[1-7]. But “emotive memory” of any event is but a psychic shadow of a past experience. Notwithstanding, recalled emotions are what drive the organism’s decision to react and act, as alluded to in some searching quotations from the American psychologist/philosopher William James (1884): “No shade of emotion is without bodily reverberations”. “Emotion dissociated from all bodily feelings is unconceivable”. “A dis-embodied human emotion is a non-entity”.

Emotions are expressed by simultaneous physiologic responses and psychic states. The literature on emotions, mentation and memory is enormous, contributed to by the likes of Aristotle, Descartes, Darwin, Freud, Spinoza, James, Cajal, Boole, Schrodinger, Turing, Chomsky, Crick and Kandel, in addition to many current physicists, cognitive scientists and evolutionary biologists (literature too vast to cite in entirety, but see refs^[6-10]). Mentation without memory would not long survive; memory without mentation could not be. Decisions to act, which are relevant to survival, are made on the basis of recalled experiences with emotive overtones.

Though we know that there is a difference between the logical and emotive modes of memory, speaking of it freely in song and

Table 1 Biomodulators of bacterial responses (feelings).	
Acetylcholine (ACh)	> 10 Universal
Amino acids (AA)	
cAMP	
Dopamine (DA)	
Epinephrine (EPI)	
Glutamine (Gln)	
Histamine (Hist)	
Norepinephrine (NE)	
Serotonin (5-HT)	
NO	

Table 2 Neurotransmitters (NTs) (feelings and emotions).	
Universal Biomodulators (> 10) (Table 1)	Specifically Neural
Neuropeptides (> 95)	
Endocannabinoids (> 5)	

verse, the mechanistic details remain obscure. Like physicists of 100 years ago, who realized that electricity and magnetism were aspects of a single phenomenon (now called “electrodynamics”^[6], as were space and time (now called “spacetime”^[7]), we realize today that emotion and memory are merged talents of “mentation”, facets of a whole process. But to comprehend these talents in a manner that is relevant to clinical medicine, we require a biochemical description, like those used to clarify the mechanisms of breathing (*i.e.*, hemoglobin), blood coagulation (*i.e.*, cascade of Factors)^[11-13].

The generally accepted model for “memory” is the binary computer chip, which however, does not operate like a biologic organism. The chip is a static piece of inorganic material which can be used to electrodynamically encode information (*info*) in binary (0/1) format, with bits organized into logical algorithms^[14-19]. But the binary code, in any physical form^[20,21] has no recourse to encoding “emotions”, which impart “meaning” or “value” to stimuli. The lack of emotive effectors in binary coding is reflected by lack of empathy and indifference to survival. For robotics, this is a key block in developing humanoid cyborgs^[22-30].

Unlike the dry electronic chip, the neuron is a metabolically dynamic cell which operates in a wet environment, employing both electrical and chemical signaling modalities. The latter evolved from the sensing and signaling capabilities of bacterial aggregates^[31-34] (Table 1). These evolved into the neural nets capable of expanded signaling modalities for encoding psychic states to render “value”, “meaning” or “significance” to incoming *cog-info*. The sensitivity of the neural system to chemicals, such as endogenous modulators (Table 1), peptides or drugs (legal and illegal) that modulate mood as well as memory^[35-42] (Table 2), speak for a chemical basis for the emotive, (psychic) state and its memory consequence.

For neural creatures, all stimuli are evaluated through the lens of “emotive values”, to decide response priority, for the well-being of the living organism.

The bacterial aggregate may not have neurons, but it has ways of signaling that is based on modulating molecules. But it does not mentate or have memory.

The neuron additionally uses a wider range of modulating molecules called neurotransmitters (NTs) (more than > 100 in total; Table 2).

The terms ‘neurotransmitter’ and ‘biomodulator’ are often used interchangeably. But they are in fact distinct classes of signaling molecules. The original bacteria signaling modulators comprise the 9 classes of biogenic amines and amino acids, as well as NO, with molecular weights smaller than 200 Daltons. Neuropeptides (NPs), which were employed by later evolving neural nets, are generally

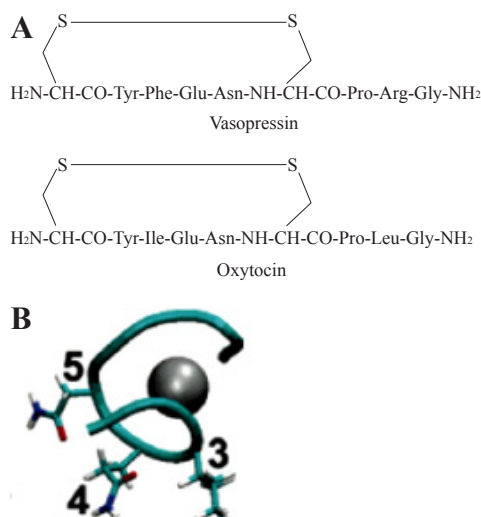


Figure 1 A: Oxytocin: the amino acid linkage forms a “tocin” ring *via* an Cys-Cys S-S closure. Vasopressin differs by 2 amino acids, but retains the same tocin ring and an affinity for metals^[46, 49]. B: A molecular model of oxytocin-Zn+2 complex^[43] (get permission).

heavier than 200 Daltons and may act indirectly, operating as switches which turn on or off signals instigated by the original biomodulators (Table 1). Administered clinically, they can elicit a wide range of physiologic and psychic responses (Table 3).

OXYTOCIN

Oxytocin^[43-49], is a nona-peptide with a “tocin” ring enclosed by an S-S linkage (Figure 1).

For example, a summary of the known effects of “oxytocin” is presented in the following list (Table 4).

The oxytocin receptor, also known as OXTR, which belongs to the GPCR -coupled receptor superfamily, is a protein that functions as receptor for the hormone and neurotransmitter oxytocin. In humans, it is encoded by the OXTR gene that has been localized to human chromosome 3p25. Oxytocin receptors present in the central nervous system modulate a variety of behaviors, including stress, love, anxiety, social behavior and memory.

NO

NO deserves special mention as it is one of the oldest, but chemically simplest signaling molecule^[50-59]. Principal bioregulatory targets for NO are metal centers in proteins. For example, NO reacts rapidly with the Co(II) of vitamin B12r to give a B12r(NO) complex with a second-order rate constant k_{on} of 7.4×10^8 M⁻¹ s⁻¹ at pH 7.4 (298 K). NO coordination with multivalent metal centers in the nECM can result in Fenton reactions (the generation of strongly oxidizing intermediates OH).

NO is unusual too; though it elicits psychic effects (*i.e.*, moods) and recall capability, it doesn’t need a receptor. NO penetrates the neural membrane directly and is involved in the expression of neural plasticity. Amazing its range of effects (Table 5), considering that it is formed from the most abundant gases in our atmosphere, O₂ and N₂.

DEFINITIONS

Before discussing details of *tripartite* mechanism of emotive neural memory^[60-64], we clarify the terms “information (*info*)” and “cognitive information (*cog-info*)”.

Table 3 Neurotransmitters and Bio-modulators of physiologic responses, that elicit both physiologic (feelings) and psychic (emotions) responses.

Bio-modulators	Ligands For metals	Physiology	Psyche
Acetylcholine (ACh)	NO	Breathing	Anxiety
Dopamine (DA)	YES	Blinking	Aggression
Epinephrine (EPI)	YES	Blood pressure	Awareness
Serotonin (5-HT)	YES	Coughing	Depression
Histamine (Hist)	YES	Crying	Fear
NO	YES	Dilation	Hate
>5 Amino acids	YES	Drooling	Heat
Nicotine	YES	Erection	Joy
Muscarine	YES	Evacuation	Love
> 95 Peptides	YES	Feeding	Pain
Endocannabinoids	YES	Fever	Sadness
		Goose-bumps	Sex
Li, Ca, Co, Cu, Fe, Mg, Mn, Ni, Sr, Zn, Al		Itching	
		Orgasm	
		Heart pulse	
(Note: The metals are the core of the complexes formed in the nECM), which also form complexes with NTs) (Figure 4).		Salivation	
		Secretion	
		Sociability	
		Spasms	
		Sweating	
		Tremors	
		Urination	
		Vasodilation	
		Vomiting	

Table 4 List of Oxytocin effects^[44-48].

Physiological Reactions
Birthing
Blood coagulation: plasminogen activator activity (PAA) and factor VIII
Lactation
Uterine contraction: cervical dilation
Wound healing
Psychic Effects
Fear and anxiety
Improved memory
Maternal bonding
Sexual arousal
Social behavior
Love
Stress

Information (*info*)

Information (*info*) can be expressed numerically and computed by logical algorithms and circuits (Squire and Kandel, 2008; Pickering, 2010; Gleick, 2011; Picard, 1997). It is ultimately physical, embodied either as an electric signal, a hole in a matrix, a magnetic spin or a photon, all representing the state of the “bit” (0/1). Computing pioneers Boole, Turing, von Neumann, Shannon, McCulloch and Pitts, designated that any input (*info*) that can be converted to binary form, is appropriate for the logical operations or algorithms performed by computers, logicians, mathematicians, programmers and some philosophers. Individual (binary “bits”) are physically embodied within the inorganic matrix of the chips, stored as bits in computers “memory”, accessed (recalled) on demand. The bit (or its loss), which represents energy ($E = kT \ln 2$ joule/bit) (Shanon 1948), has no emotive signifier or meaning; each bit is like the other; none has inherent value/significance. In “computation”, sets of bits are assembled from input and processed by logical (linguistic/mathematical) algorithms, to compute output (see Turing machine) (Wikipedia).

Thus, Boole’s and Turing’s binary-based *info* and associated algorithms (Milo *et al.*, 2002; Anastassiou *et al.*, 2011) are emotionally

“blind”; they lack emotive signifiers are demotive. By contrast, neural *cog-info* is rich in emotive content and psychic experience. It is based on the multiple emotive effects that can be elicited by biomodulators and NTs (Tables 1-3). The binary coding of “*info*” is but a pale shadow, compared to the richness of the emotive encoding of “*cog-info*” (Equation 1), 2-D vs n-D (where $n > 100$).

Equation 1: $\text{Info (bit)} \neq \text{Cog-info (cuiinfo)}$

type: $\text{logical} \quad \text{logical} + \text{emotive}$

dimensions: $2\text{-D} \quad n\text{-D}$

It is said that physics and logic alone cannot address subjective “value” of psychic states experienced as feelings and the recall of such (emotions). We opine that chemistry is the appropriate discipline to address such issues, as it is for various medical conditions. The questions and answers to the “enigma of memory”, must be couched in biochemical terms. Proposed models of neural memory must employ components available to the cell, in an aqueous milieu with low energy but high capacity and encoding complexity.

Tripartite mechanism^[60-64]: To that end, we begin by recognizing physiologic reality: The neuron is not “naked”, not floating in empty “space”, as suggested by histological images and renderings by Cajal, repeated in many textbooks, websites and magazine covers (Figure 2). Though each neuron is unique...different from all others, all are enswathed in a functioning neural extracellular matrix (nECM)^[65-70], a hydrogel that is “doped” with diffusible metals.

For the purposes of our discussions, we merge all cellular entities (astrocytes, glia as well as neurons) under the umbrella term of “neuron”. Admittedly, astrocytes and glia cells are important for proper neural functioning^[71-73]. But focusing only on cells, as by optogenetic coloring^[74], while ignoring their surroundings, leaves out a crucial aspect of their ability to perform a mental function (i.e. memory). Their synaptic contacts must be considered in light of the fact that most neural dendrites do not make synaptic contact with other neurons, but establish non-synaptic signaling through

Table 5 Nitric oxide (NO), a multi-tasked signaling molecule^[50-59].

Field	Mental and Physical Effect
Physiology	Blood pressure, itching, pulse, salivation, sweating, breathing
Biochemistry	Bind transition metals, Fenton reactive (generates free radicals), forms metal-centered ternary complexes, soluble in lipids, nitrosylates proteins and other substrates
Neurology	Affects memory, learning, permeates cell membranes, connected to ATP metabolism, modulates synaptic plasticity
Psychology	Anxiety, depression, fear, laughing, mood, sociability
Clinical aspects	Alzheimer, Parkinsons, autism, bipolar disorders

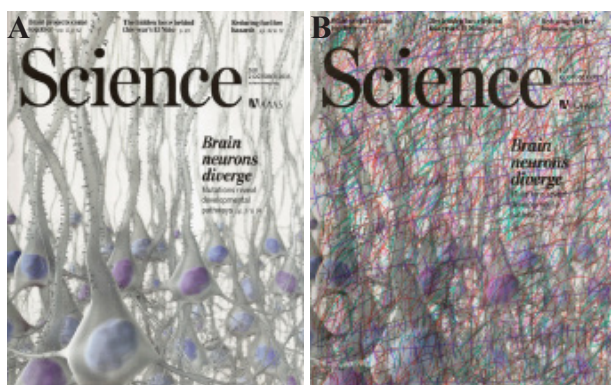


Figure 2 A: Neuron depicted in a recent Science^[77], suspended in empty space (“naked neurons”) (reproduced with permission of AAAS); B: Tripartite corrected image, with overdrawn lines representing the nECM lattice around the neurons, wherein fluid, with metals and neurotransmitters (NTs) can diffuse.

the nECM^[75,76]. The dopants released from neural vesicles into the nECM, affect the synaptic and non-synaptic chemical signaling (volume transmission) between neurons and interactions with the nECM.

In our previous publications, we referred to many citations of metals in the brain, The presence and effects of neurotransmitters (NTs) in the brain is also well documented and referred to in many textbooks and publications, of which we cite a few.

An example of current representation of neurons is given in Figure 2A. It is conventional in that it leaves the neurons suspended in empty space. We graphically augmented the nECM in Figure 2B to emphasize its role as the surrounding “memory material”, wherein neurons encode and store cognitive information with metals and NTs.

The surrounding nECM is a missing component in most schematic representations of neural signaling. We graphically added the nECM in Figure 2B, to emphasize its role as the surrounding “memory material”, wherein neurons encode and store cognitive information with metals and NTs. Illustrating only the neurons in monotone or as a multicolor “rainbow”^[74], overlooks a key aspect of neuron mental processing.

Cognitive information (*cog-info*)

Cognitive information (*cog-info*) is analogue (not digital); associated with simultaneous physiologic and psychic arousal states, remembered as emotions (fear, pain, anxiety, love, hunger, sex, *etc.*). *Cog-info* sometimes may be logical, notably in mathematics and the physical sciences. But it can also carry emotive significance.

Q: What formalism permits the encoding of emotion?

A: Morse and Braille codes, as well as all binary encoded algorithms, are emotionally barren. Words aside, music notation is our only example of emotive sound reduced to (encoded as) a graphic notation (notes): Song (or melody) has been graphically represented, with specialized notations developed by different

cultures. The point is that musical sound can be encoded as written scripts, which can be read and replayed by skilled musicians. The notations of tone and timing represent the enciphered memory of sound which can elicit an emotional response from the audience, an example for the encoding of neural emotive experience.

Feelings and emotions

The terms “feeling” and “emotion” are often used interchangeably. However, they are distinct terms: “Feelings” relate literally to bodily sensations (light, sound, pain, balance, hunger, thirst, *etc.*) generated by specific sensors to outside stimuli, which are accompanied by bodily reactions and corresponding psychic states (Table 1).

Q: How are emotions related to feelings?

A: Feelings are immediate perceptions from our senses, physiologic reactions to external stimuli that have coincident psychic effects. Emotions are a replay of remembered feelings, psychic experiences that are concomitantly manifest (accompanied) by physiologic reactions. “Emotions” can be said to be remembered “feelings”.

Though a feeling (sensation) can be digitized by a silico sensor (*i.e.*, photoelectric cell, microphone, pressure transducer, *etc.*), such digital description lacks the psychic impact of neural emotive states.

The encoding, storing and decoding of emotive cognitive information within the brain is a mental talent that emerges from the interplay of individual neurons each other as well as with their immediate surroundings, the nECM as a “memory material”. The neurons employ the NTs as molecular effectors of both physiologic and psychic responses, encoded as described by the *tripartite* mechanism.

Emotions cannot be encoded with 0 and 1. A binary ($n = 2$) computational explanation of neural memory misses the complexity of a chemically based “multinary “ ($n > 10$) neural code which permits of psychic experience (emotions) and memory thereof. This is not simply a difference in styles (*i.e.*, digital vs analogue), but requires a paradigm shift^[78].

“Recalled feelings”, namely “emotions”, are relevant to the survival of the neural creature. Whereas “feelings” only require current physical stimuli, as for example experienced by a bacterial aggregate, “emotions” operate through memory. Emotions, a talent of neural creatures, endow value/meaning to incoming *cog-info*, remembered and recalled to determine behavior. This a crucial difference between the binary *info* of the computer and the multinary *cog-info* of the neural net. The former cannot encode emotion, the latter must, to survive.

Consider that small molecules which modulate the tropisms of micro-organisms, bacteria and plants, also modulate the behavior of animals with nerves. They are the universal biomodulators of all physiologic systems (Table 1). We propose that the NTs have been adapted to serve the evolving multiple functions of neural networks. Biomodulators were initially composed only of biogenic amines, later developing specialized neuro-peptides, also served

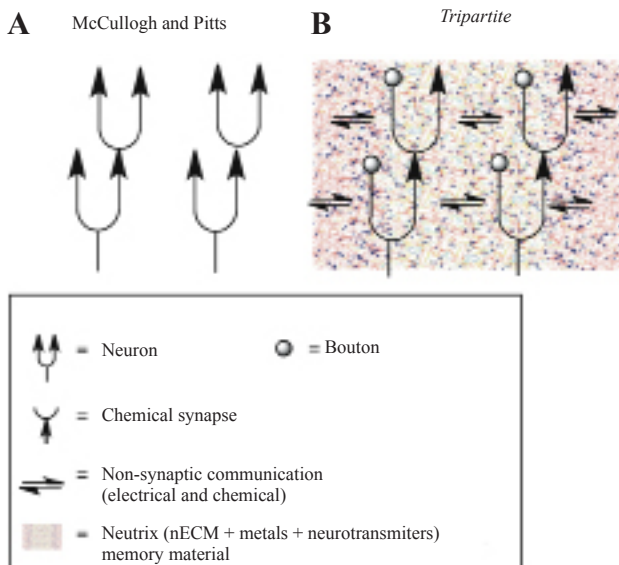


Figure 3 Schematics of neural environment and cell signaling: A: McCulloch & Pitts' 3-neuron electric signaling, with synaptic contacts occurring at arrowhead points^[6]. Note the “naked neurons” ignoring the nECM; B: Corrected Tripartite 3-neuron network immersed in nECM, doped with diffusible metals and NTs. The intimate non-synaptic contacts between the neuron and the nECM, permits chemical as well as electric signaling.

as signaling molecules (Table 2). There are clear links between the ability of NTs to elicit a range of physiologic responses (feelings) and to modulate psychic experiences (emotions/moods/psychic states) (Table 1). The NTs are the “smoking guns” of emotive mentation and memory; they elicit physiologic responses associated with psychic states, which are remembered as emotions.

We propose a *tripartite* mechanism^[60-64] to describe the most basic aspects for chemically encoding, storing and decoding *cog-info*, focusing on the interactions of three physiologic compartments, namely:

Neurons - spindly, elongated synaptically and non-synaptically signaling cells, all suspended in nECM + dopants, with some synaptic contacts. Other cells, such as astrocytes and glia, are also involved in great number, but they can be classified as “helper cells”, which enable to functioning of the neural net^[71-73].

nECM- neural extracellular matrix a hydrogel lattice, comprised of block-copolymers of anionic glycosaminoglycans (GAG) and proteins ensnaring all neurons^[65-70].

Dopants - Metals + neurotransmitters (NTs) within the nECM, used by the neurons to encode/decode *cog-info*.

BIBLIOGRAPHIC HISTORY

In Part 1 of this series, we outlined the general features of the *tripartite* memory mechanism with only metals. We proposed that the [nECM: Metal] complex serves to encode a minimal cognitive unit of information (*cuinfo*) (singular/plural), the molecular correlate of *cog-info* derived from the stimulated senses. The neuron and neural circuits employ the nECM with diffusible metals to encode and store many ensembles of *cuinfo*, from which memory is evoked. Effectively, memory is stored not as a reverberating electric signal (Figure 3A), but as physical *cuinfo* within the nECM lattice around the neuron (Figure 3B).

We cite the Vizi work^[75,76] to focus on experimental facts...most dendrites do not make synaptic contact but peter out into the nECM.

The extensive contacts between the neuron and the nECM cannot be ignored. Thus, we provide an overarching rationale for this, namely the *tripartite* mechanism which provides a biochemical description of neural processes whereby memory is encoded in the nECM.

Our point in Figures 2 and 3 is that illustrating only the neurons (in monotone or as a multicolor “rainbow”) overlooks a key aspect of neuron mental function. The surrounding nECM is a missing component in the schematic representation of neural signaling, the basis for memory and mentation.

It has previously been suggested that “holes” induced in the nECM by enzymes could be used by neurons to encode and store *cog-info*^[70]. But we are not satisfied that this is a credible encoding process. Left hanging are questions regarding the size of the holes, how are they formed, what controls the enzymatic processes. Ultimately, the hole /non-hole aspect is similar to a binary coding system like Braille, and does not account for emotions. But at least Tsien is looking in the right direction...focusing on the nECM around the neuron.

As an alternative, we have suggested a *tripartite* mechanism citing 8 sets of confirmatory observations, including: Memory loss (forgetting) correlated with inappropriate levels (toxicity/deficiency) of diffusible metals (Al, Ca, Co, Cu, Fe, Hg, Li, Mg, Mn, Pb, Zn *etc*); the improper functioning of the nECM, exemplified by experiments with knock-out mice lacking tenascins or immuno-depletion of metal transporters, metallothioneins. Of course, malfunctioning of the neural circuit (Figure 2B) due to either nECM degradation, or loss of neural circuit integrity, also correlate with memory loss (forgetting).

The focus of MBM Parts 2 in this series was on the chemistry of metal-centered complexes (Marx & Gilon, 2013 a). We reviewed the multiple ligands available in the saccharide subunits of the nECM (GAGs: chondroitins, heparans, hyaluronates), as well as proteins (tenascin, laminin and fibronectin), for metal binding to form *cuinfo*. We described other types of chemical (Fenton redox, cross-linking) reactions to affect tagging and stabilizing of the *cuinfo*.

Expanding this theme in Part 3, we further proposed that NTs are the molecules that encode emotive value/meaning/ significance to neural memory of feelings. Their affinity for metals renders NTs susceptible to complexation by *cuinfo*, thereby “flavoring” them with emotive signifiers.

A chemical notation (“chemography”) for the encoding of cognitive units of information (*cuinfo*) is presented in Figure 3.

We provided extensive citations for experimental finding of metal levels in brain tissue and neurons^[60]. The presence of NTs in neurons (*i.e.*, glutamate, histidine, serotonin, DOPA, etc) is described in many current publications (to numerous to cite here). To aid consideration of this point, we refer to Table 3 which summarizes the physiologic and psychic effects of numerous NTs.

MBM Pt 4^[64] compared brain to computer. We focused on a multinary “information theory” for “cognitive information” appropriate to neural systems. We estimated the capacity of the brain in molar, avogadro terms (6×10^{23}).

Here, we focus again on emotions, considering the NTs to be modulators of simultaneous physiologic and psychic responses (Tables 1, 2). Most NTs are metal chelators, packaged together with metals in neural vesicles; co-secreted into the nECM during neural chemical signaling. Consequently, they are available to encode *cog-info* in the nECM via metal-centered complexes. The *cuinfo* can anchor an NT to the nECM by forming a metal-centered complex, a *cuinfo* with emotive value/meaning.

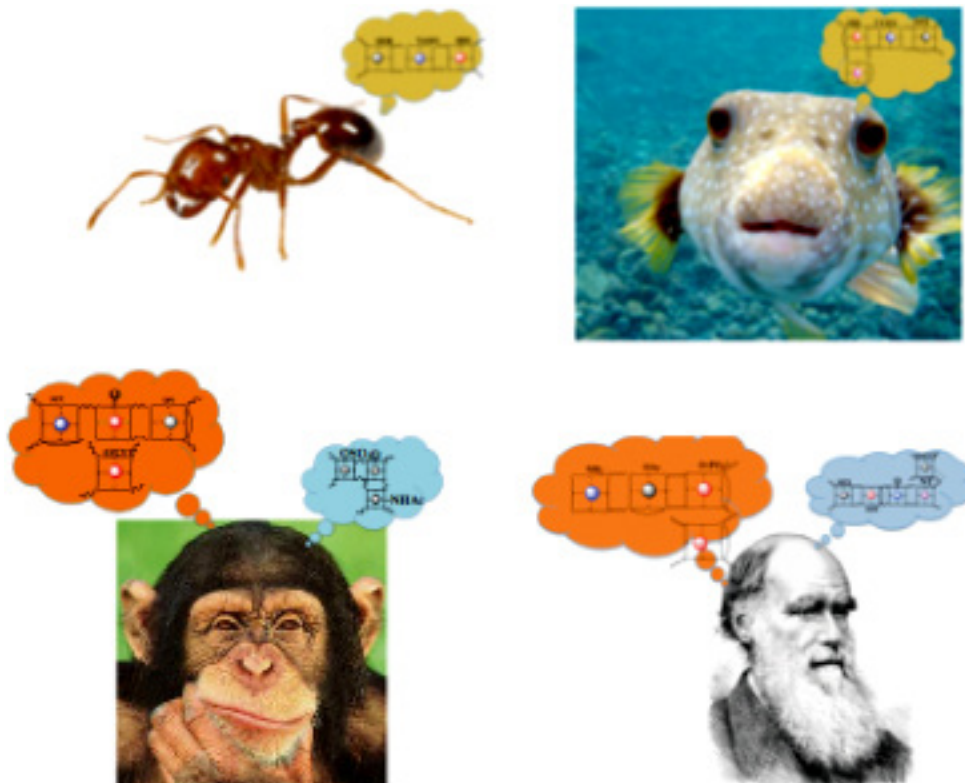


Figure 4 Iconographic examples of cuinfo based memory of the ant, fish and chimp. The ant and primitive fish exclusively employ emotive modes ; the chimp employs both emotive (with NTs) and logical modes (without NTs).

EVOLUTION OF MEMORY MODES

From an evolutionary perspective, the functionalities of bacterial biomodulators and cognate receptors were expanded, to meet the needs of the ever-more-complex signaling needs of the evolving neural structure and circuitry. Eventually, neuropeptides were also adapted to modulate the abilities of neural nets to perform ever more subtle feats of mentation and memory, colored/flavored/tinted by emotions. Possibly, they exert their effects indirectly, through the agency of the biogenic amines.

Mechanistically, one could consider that the bacterial biomodulators constitute signals which designate the bacterial colony’s sensing (feeling) the environment. Similarly, neural “feelings” are also accompanied by immediate physiologic reactions involving the identical signaling molecules and others called NTs (Table 2), which all elicit psychic states out of the neural net. Thus, “feelings” are sensate and immediate; “emotions” are recalled “feelings” of a past psychic state.

To encapsulate our ideas regarding a read/write mechanism, we propose that vesicle release from neurons into the nECM serves as a write mechanism to encode cognitive information in an accessible, but stable place. To “read”, the neurons employ surface mobile sensors (such as GPCR mosaics, K channels and ACholR) which are exposed to the nECM, to sense the encoded cognitive information.

Biology is conservative, it generally adopts existing molecules, structures and processes, to perform ever more complicated functions for evolving organisms. Experimental evidence reveals that biologic memory of higher animals evolved from earlier versions [79-85]. For example, bacteria express a number of universal modulators that for neurons we also term “neurotransmitters” (NTs), many of these being peptides and their cognate receptors (Tables 1 and 2). Though bacteria and plants, employ chemical

signaling processes, they cannot be said to have memory.

Chemical signaling by bacteria and cell aggregaters preceded electrodynamic synaptic neural signaling by > 700 million years. The emergence of the neural system evolved in the preCambian period (~ 500 mya)^[84,85] the mammalian brain arose around 300 mya (Rowe *et al.*, 2011). In the parsimony of Nature, it is not surprising that chemical signaling was retained by the evolving neural net. The snail, ant and bee with neural nets but no brains exhibit memory based on emotive responses to stimuli (pain, smell, food, sex, heat, *etc.*) associated with molecular modulators released from neural vesicles. These simultaneously modulate physiologic reactions and elicit emotional responses, which are recalled as emotive memory (Figure 4).

The evolutionary biology of mentation and memory needs to take into account the limitations and possibilities of neural morphology, as well as the materials and processes, available to the neurons. Figure 4 represents that animals without brains but with neural nets (ganglia) (ants, flies, bees, snails), remember past stimuli.

Simple calculation indicate that the nECM combined with metals and NTs provides the neural system with astronomic, options for encoding cog-info, combinatorials of Avogadro (10^{23}). The psychic sensations (feelings and emotions) confer meaning/value/significance to cog-info relevant to survival and reproduction^[64].

We emphasize that the neuron and its signaling network evolved from the bacterial signaling systems (GPCR, K-channels and AChR) to eventually perform ever more subtle feats of memory. All animals capable of manifesting memory (Figure 5), employ a neural net (ganglion or brain), whose neurons are enswathed in nECM (~15-25% brain volume), along with diffusible “dopants” of metals and NTs. The NTs are molecular linkers that mediate autonomic responses, linking physical reactions and psychic perceptions experienced as emotions. These are literally imprinted in memory

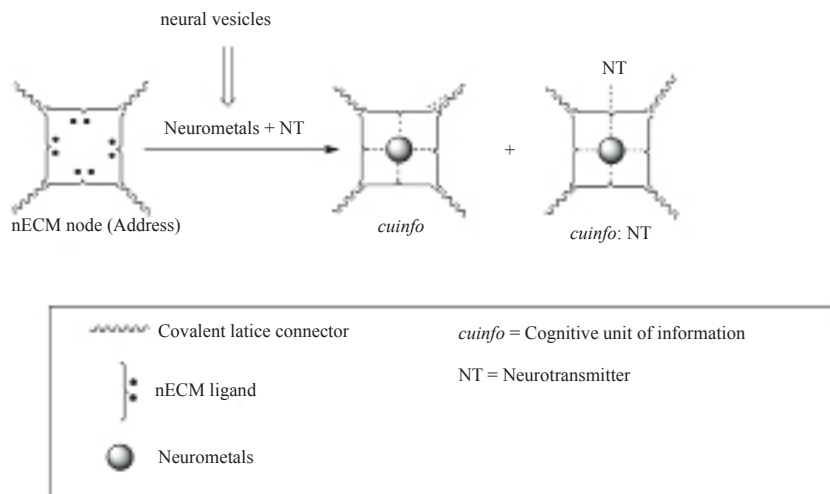


Figure 5 Chemographic representations of the reaction of an nECM (electron rich) site or “address”. The binding of a metal and a neurotransmitter (NT), encodes logical and emotive units of memory, respectively.

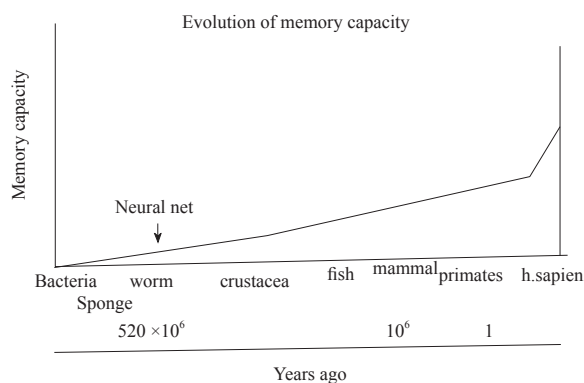


Figure 6 Schematic of the evolution of memory capacity in different organisms. (adapted from Krubitzer, 2009; Strausfeld & Hirth, 2015).

by adsorbed NTs, their traces decoded as recall. The earliest forms of memory were exclusively chemically emotive, whose recall conferred survival value. Only late in evolution, did the neural system develop non-emotive process for remembering objective (logical) *cog-info*. The latter mode increased dramatically in man with the evolution of the talent for language.

Regarding a read/write mechanism, we propose that vesicle release from neurons into the nECM serves as a write mechanism to encode cognitive information in an accessible, but stable place, the nECM around the neuron. To “read”, the neurons employ surface mobile sensors (such as GPCR mosaics, K channels and ACholR) which are exposed to the nECM, to sense the encoded cognitive information. In the interests of space and focus, we defer further discussion of the “read/write” processes employed by the neuron, for another venue.

DISCUSSION

It is said that physics and logic alone cannot address questions related to value or to subjective phenomena such as emotions. The electronic computer is an inadequate model. Though philosophers, novelists and songwriters have tried to bridge the gap between “emotion” and “logical” thought, there is no generally accepted model of the “emotional process” nor an encoding capability for such.

We opine that chemistry is the appropriate discipline to

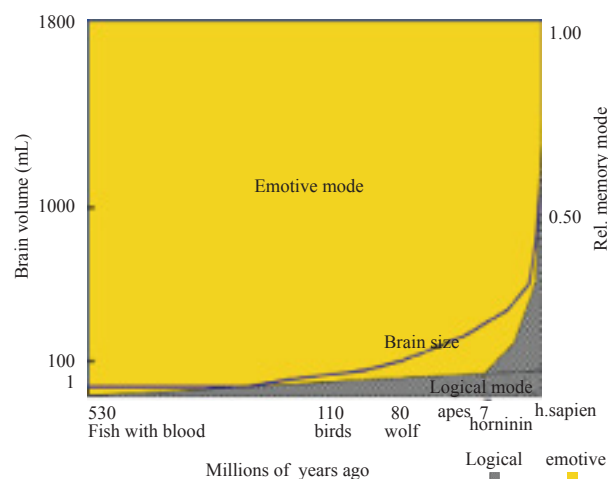


Figure 7 Evolution of 2 modes of memory/mentation correlated to brain/skull size. Most animal mentation operates in an emotive mode, whereas the logical mode emerged at a relatively late stage in the evolution of land animals, as a mentation “phase change” (brain/skull size adapted from^[8,10]. Human mentation is arbitrarily set as ~60% emotive but it could be higher, as the value or significance of any stimulus is established by emotive codes.

address the enigma of the “emotions” as they pertain to memory. The discourse must be couched in chemical terms appropriate to all other physiologic processes. Darwinian evolutionary considerations suggest that NTs which modulate trophic responses in the developing brain, were adapted to modulate new signaling functions and capacity of neural creatures (Figure 6).

The logical *cuinfo*-based memory with no emotive content (rational), was a late evolutionary trend particularly manifest in man with a talent for language. The development of a brain operating in emotive and logical modes of memory and mentation, suggests a “phase” diagram (Figure 7) wherein the logical mode emerges coincident with increasing brain size and complexity (Johnson, 2001).

But it all started with emotive signaling and responses. The logical mode, which erupted with the rise of language, was a very late development. That is why we have to struggle to retain memory of logical operations; not everyone is up to it. But the emotive response and the memory thereof are common to all and easily remembered.

Q: How does a neural organism establish the relative importance/significance for one particular set of stimuli over others?

A: In the neural system, significance/value/meaning/priority are synonymous, all established by the yardstick of survival. Emotive values encoded by NTs, which provide a basis for prioritizing and remembering significant events out of the welter of stimuli constantly bombarding the organism, from which decisions are made.

One can consider that most animal memory is emotive; the logical mode was a relatively late development of brained animals, to more effectively achieve emotionally-desired/valued goals.

Verbalization is a unique human capability closely associated with logical thinking empowered by words. Language also provides greatly amplified memory capacity, with high resolution conferred by recalled words. A logical (rational) memory mode, operative in an animal, is evinced by a few behavioral (objective) criteria, such as: Use of tools; Group hunting; Teaching the young; Group communication; Verbalization (language).

In neural creatures, memory is flavored with emotions, tinged by physiologic reactions. Even in man, valuation, goals and decision-making are all based on emotive factors. Only in mathematics, programming, and philosophy are the logical modes of memory and mentation dominant, excluding emotive content. Logic is not driven to perform; rather, it serves the goals/desires/values established by emotion. Phrases such as “affective coding” or a “rational emotion”^[24-29] are beside the point. Whereas a rational (logical) algorithm can be programmed into a binary Turing machine, the emotional affective) psychic states cannot be encoded, much less programmed; it must be experienced by living creatures.

CONCLUSION

The reaction of a metal cation with an anionic locale (address) within the nECM forms a [nECM: Metal] complex, a cognitive unit of information (*cuinfo*). Such encoding is similar to the encoding of a logical, binary bit ($n = 2$), but has greater dimensionality ($n > 10$), as it includes a covey of > 90 NTs, capable of encoding feelings/emotions.

Unlike binary computer memory that operates exclusively in binary code, neural memory is expressed in multinary “emotive”, as well as “logical” states. The nECM functions as a “memory material” to which the neuron is intimately exposed by virtue of its extended, arborized shape. The NTs which instigate physiologic responses, also elicit emotional reactions and encode psychic, emotive states in memory.

Q: Is the *cuinfo* employed by the neuron equivalent to a “bit” processed by a computer?

A: The *cuinfo* is much more than an information bit (see Equ. 1); its processing effectiveness is manifold greater, enriched by emotive signifiers (Table 3). It encodes “cognitive information” rich with emotive overtones. Biologic mentation and memory operates in a multinary, combinatorial manner as-yet-undreamed of by programmers limited to the binary algorithms of Boole, Turing, Shannon, *etc.*, which only employ 2 “objective” signifiers (0 1).

We aspire to a “leap of reason”, to comprehend the emotive and logical workings of our brains in molecular terms, consonant with the morphology of neurons and the availability of components. Though it is said that God (or for some), the devil is in the detail, we propose a bimodal tripartite mechanism to detail the emotive and logical talents for encoding neural memory with chemographic representation, but without ghosts or spirits.

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CONFLICT OF INTEREST

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

CG is emeritus professor of HU, but is active in developing and patenting peptide-based tools for surgery and pharmacology.

Notwithstanding, the ideas forwarded here are scientifically genuine and presented in good faith, without commercial clouding of the concepts expressed here.

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