Published online: June 30, 2019

Short communication

The *tripartite* mechanism as the basis for a biochemical memory engram

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DOI: 10.31083/j.jin.2019.02.6101

In this paper, we address the enigma of the memory engram, the physical trace of memory in terms of its composition, processes, and location. A neurochemical approach assumes that neural processes hinge on the same terms used to describe the biochemical functioning of other biological tissues and organs. We define a biochemical process, a *tripartite* mechanism involving the interactions of neurons with their neural extracellular matrix, trace metals, and neurotransmitters as the basis of a biochemical memory engram. The latter inextricably link physiological responses, including sensations with affective states, such as emotions.

Keywords

Cognitive information; affective biochemistry; trace metals; neurotransmitters; extracellular matrix; memory engram; emotive memory

1. Introduction

The notion that the basis for memory was due to physical changes in the brain, was first proposed by Semon (~1900), who also coined the term "engram" to refer to the physical trace of memory. However, subsequent generations of neuroscientists have not succeeded in localizing the trace in the brain: the "engram" seems to be distributed throughout the brain (see Lashley, 1950).

Contemporary views on the mechanisms of memory and what the engram means have proposed that dendritic spines represent the basic unit for memory storage, or suggested that memory retrieval involved gene expression leading to protein synthesis and structural modifications of the synapse, or the idea that increased electrodynamic signaling at the synapses was key to the emergence of memory and learning, while retaining the engram at the level of cell morphology (cell ensembles, spines, synapses) (Poo et al., 2016).

Similarly, others hypothesized that clusters of stationary, local and permanent electrical pulses are the signatures of enduring memories which are imprinted through nonsynaptic plasticity (Cacha et al., 2017). None considered molecular scaled processes or chemo-dynamic signaling.

2. *Tripartite* mechanism of memory

Neuroscientists from the time of Cajal and Hebb enunciated a theory of "synaptic plasticity" where the basis of learning and memory was ascribed to the increased number and functionality of neural synaptic connections (Kandel et al., 2012; Mishkin and Appenzeller, 1987; Squire and Kandel, 2008). In modern clinical medicine and neural biology, it is generally accepted that neural mental processes are based on chemical processes (Brady et al., 2011). But what are the details?

In a series of papers, Marx and Gilon (2012, 2013) suggested a biochemical *tripartite* mechanism whereby neurons could encode the cognitive information incoming from the senses, into a chemical code that serves as a basis for the molecular basis of memory. They outlined the concept and graphic representation of the *tripartite* mechanism describing chemical reactions involved in various processes that underlie the *tripartite* mechanism. It specifies that the neurons interact with the surrounding neural extracellular matrix (nECM) with dopants (trace metals and neurotransmitters (NTs) to generate a biochemical neural code as "cognitive units of information" (*cuinfo*) within the nECM.

Hebb (1949) enunciated a theory of "synaptic plasticity" as the basis of learning and memory, ascribed to the increased number and functionality of neural synaptic contacts, a "reverberating circuit" which is still popular among neuroscientists (Kandel et al., 2012, 2014). Subsequently, Hebb's was accused of seven "sins"; failing to address many issues critical to modeling neural memory (Arshavsky, 2006). To redeem these "sins", we offered the *tripartite* mechanism whereby *cuinfo* (the neural "memory material") are encoded as metal-centered complexes within the nECM, around the neurons. .

Marx and Gilon (2014) described combinatorially diverse encoding options (multinary) with > 10 trace metals and > 90 neurotransmitters (NTs) for "flavoring" *cuinfo* with emotive tags used for retrieval. We pointed out that the NTs are a class of molecules synthesized and secreted by neurons that elicit emotive reactions, concomitant with physiologic responses (i.e., entangled). Thus, NTs can be considered as the molecular embodiments of "sensations" recalled as "emotions".

Marx and Gilon (2016) described a physiologically credible code for emotions psychic states (emotions) as well as physiologic responses (e.g., sensation). Both are encoded with biomodulators (neurotransmitters) which can bind to metal-centered *cuinfo*, lit-

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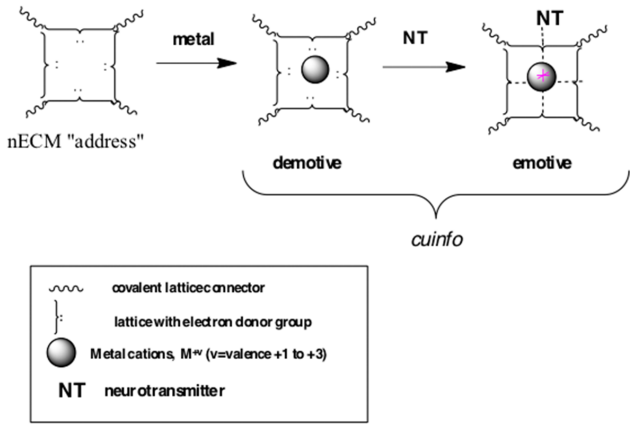

Figure 1. Chemo-graphic representations of the reaction of an nECM binding site for a metal cation, an "address". The binding of a NTs to the metal-centered *cuinfo* confers an emotive context (Adapted from Marx and Gilon, 2016).

erally 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 (Tosches et al., 2018). Thus, the *tripartite* mechanism permits a chemical perspective on the evolution of "logical" and "emotive" modes of neural memory. As well, the proposed *tripartite* mechanism describes a chemical code for affective states that is not linguistic but presents the molecular correlates of the epigenetic "engram" (Cacha et al., 2017) that render the neural synapse operative for the function of recall.

We expect that the molecular-scale encoding/decoding process must be faster than the rate of neural firing ($<$ 100 ms) (see Table 1). Also, the rates of macromolecule elongation or translation are too slow to account for the speed of memory acquisition or recall. Clearly, the rates of protein synthesis and DNA/RNA elongation are too slow to serve as effectors of neural memory, which must be faster than 0.1 sec, at least for short term memory. Thus, structural modifications of the synapse do not account for short-term memory formation. By contrast, metal complexation reactions and the binding of NTs are fast reactions and do not require high energy (Brady et al., 2011).

The neuron is suspended in a web of nECM. It instigates the formation of metal-centered complexes within the nECM, which are equivalent to "*cuinfo*" (This is because cuinfo has already been defined), represented as chemo-graphic icons (see Fig. 1). This is a very rapid process that requires little energy (see Table 1). For the purposes of our brief report, 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. But 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 (ephaptic) contacts through the nECM (Arellano et al., 2007; Vizi et al., 2010; Vizi, 2013).

Table 1. Kinetics of various neural processes.

Process	Time scale
Protein chain synthesis	10^{-1} sec per amino acid
RNA elongation	10^{-2} sec per base
DNA elongation	10^{-3} sec per base
Neural firing rate	10^{-2} sec
Neuro-electric impulse	1-100 m/sec
Neural GPCR receptor diffusion	10^{-1} to 10^{-3} μm^2 sec^{-1}
Ca^{+2} diffusion in nECM	2.3×10^{-6} cm^2/s
Molecular binding events	10^{-7} sec
Protein turnover (replacement)	3 months
Mosaic diffusion over neural surface	10^{-1} to 10^{-3} μm^2/sec
Ionic memory chip byte encoding	10^{-7} sec

3. The neural extracellular matrix

Unlike depictions in most textbooks, neurons are not "naked". They are surrounded by a web of hydrated glycosaminoglycans (GAGs) termed neural extracellular matrix (nECM) comprised of a mix of polysaccharides (chondroitin, hyaluronates heparans, GAGs) admixed with accessory proteins (i.e. tenascins, collagen) (Bogoch, 1968; Cserr, 1986; Iwata and Carlson, 1993; Kamali and Nicholson, 2013; Schmitt et al., 1969). Thus, the neuron is not "naked", but clothed in a filigree of GAGs. The intimate con-tacts of the extended neural surface with the nECM permits signal recognition between the neuron and the nECM (Katchalski, 1992). It should be noted that the nECM is much less prone to biodegra-dation than proteins and protected from such decay (Golgolla et al., 2009). For example, the backbone of DNA is comprised of a protected polysaccharide (poly-deoxyribose) which lasts a life-time.

More than ten trace metal cations are dispersed within the gross brain tissue as well as within the individual neurons to mM levels (Becker et al., 2005; Becker, 2010; Popescu et al., 2009). Most metals were found within the neuron, particularly the nucleus. They are also present in the nECM, at levels ranging from 10^{-6} to 10^{-9} M. Trace metals cations are transported into the neurons via metallothioneins (Fischer and Davie, 1998; Kägi and Schäffer, 1988; Suzuki et al., 1993). In the nucleus, they participate in the processing of DNA into RNA into proteins which also involves tubulins (Watson et al., 2013). In the neuron's cytoplasm, they are involved in cell metabolism. They are also loaded into vesicles for eventual release. To the extent that intracellular metals are collected into vesicles to be expelled into the extracellular nECM, both metal pools can be considered to work in combination with the nECM. As well the chemistry of the nECM (many anionic pockets) predisposes it to react with metal cations. In effect, the neuron employs the nECM as a matrix wherein it can use metal cations and NTs to encode cognitive information, by ejecting vesicles containing metal cations and NTs, to form *cuinfo*.

Monovalent metals form short-lived, unstable complexes. Divalent and polyvalent metals form complexes that are inherently more stable. For example, we provide chemo-graphic representations of *cuinfo* undergoing "tagging" and crosslinking reactions, essential for indexing *cuinfo* for organized storage and retrieval. Monovalent metals form relatively unstable nECM com-

plexes (might be associated with short term memory); whereas polyvalent metals are generally more stable (might be associated with long term memory). Metal complexes of "memory units" are much more stable than any achieved by H-bonds in an aqueous environment. Thus, the suggestion that H-bonding encode memory (Amtul and Rahman, 2016) is not appropriate. The entire neural net is immersed in an aqueous environment. Indeed, hydrogen bonds are involved in establishing the structures of proteins and DNA. But hydrogen bonding for polysaccharides in an aqueous system is too labile to serve as a coding system. Also, hydrogen bonding is bereft of emotional content. It is like the binary code locked in 2-D materiality.

The terms "neurotransmitter" and "biomodulator" are often used interchangeably. But they are in fact distinct classes of signaling molecules (Reith, 2002; Roshchina, 2010). The original bacteria signaling modulators comprise the nine modulators including biogenic amines and amino acids, with molecular weights smaller than 200 Daltons. Neuropeptides, which were employed by later evolved neural creatures, are generally heavier than 200 Daltons and may act directly in synaptic as well as non-synaptic signaling. They can also operate as switches which turn on or off signals instigated by the original bacterial biomodulators (Roshchina, 2010). It is an established fact that NTs inextricably link (entangle) physiologic responses (e.g., sensations) with affective states, termed "emotions" (Mesulam, 1998).

The mature neuron is surrounded by nECM during its development. To "write", the stimulated neuron containing dopants ejects into the already existing surrounding nECM (Budnik et al., 2016; Davis and Muller, 2015; Kay et al., 2006; van Niel et al., 2018). The neuron thereby forms sets of metal-centered complexes within the surrounding nECM, therein rapidly encoding *cuinfo* (see Fig. 2). To the extent that the *cuinfo* is physical (chemical complexes), they

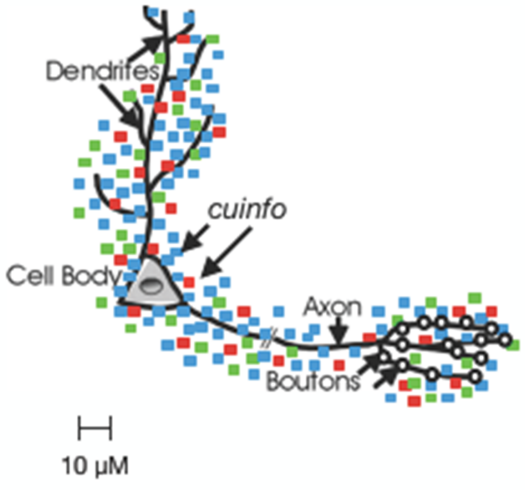

Figure 2. The neuron is surrounded by nECM (GAG lattice not shown) which serves as a neurochemical "library" wherein units of encoded memories are stored as *cuinfo*. The colored boxes representing the individual *cuinfo* described in Figure 1, are not to scale, as they are of molecular dimension (i.e. 10 nm) compared to the 10-100 μm scale of the neuron and its parts. The different colors indicate complexes with different combinations of NTs and metal cations.

embody the "engram", the physical trace of memory first hypothesized by Semon (Kim et al., 2018; Lashley, 1950; Santoro and Frankland, 2014; Schacter, 2011; Semon, 1923). The epigenetic *cuinfo* (engrams) of memory (Cacha et al., 2017) are distributed over the whole brain as a guiding template. While there may be specific cells involved in encoding and retrieving the engrams (Roy et al., 2016), the *tripartite* mechanism posits that the physical traces of the engram are distributed in the nECM around the neurons (see Fig. 2).

To "read" or decode the *cuinfo*, the neuron employs at 3 types of "sensors", aggregates of proteins (i.e. mosaics embedded within its membrane, examples being GPCR mosaics, K2P channels and acetylcholine receptors (AcCholR)), all which number many thousands per neuron (Corringer et al., 2012; Juliano and Haskill, 1993; Katchalski, 1992; Lobmaier et al., 2001; Zhang et al., 2012). They perform as mobile chemo-dynamic sensors (reported diffusion: 10^{-1} to 10^{-3} μm^2/sec) (Choquet and Triller, 2013; Triller and Choquet, 2005), which transform the chemical code of *cuinfo* around individual neurons, into neural signals (Roy et al., 2016), ultimately processed by the neural net and experienced as coherent emotive memory. The neural code which forms memory is instigated by the signal input of cognitive information from each of the senses, with each input encoded by a *tripartite* mechanism. The neural net integrates (consolidates) all the *tripartite* units to generate a composite mental pattern manifested as comprehensible, emotive memory.

4. Discussion

Earlier attempts have been made to locate the engram in a brain structure concluding that the engram is not localized, but distributed throughout the brain (Lashley, 1950). Others identified groups of cells termed "engram neurons", as their electrical firing correlated with recall. Some considered "resonating circuits" as the basis of the engram. That is, neural synaptic contacts are "strengthened" when a signal continues to impact them. These circuit provides stronger and stronger *resonant* signals as time pass. All these are predicated on a model of exclusive synaptic signaling between neurons, to which objections have been raised (Arshavsky, 2006). In particular, it ignores the non-synaptic (ephaptic, volume transmission) signaling that is also a feature of neural communication (Agnati et al., 2004; Vargova and Sykova, 2014; Vizi et al., 2010; Vizi, 2013).

The concept of "resonance" is of interest to chemists as it relates the idea that in some molecules the electrons are not located at a specific bond (i.e. conjugated double bonds) but can be "delocalized" (smeared out). The "resonance" phenomenon is not limited only to molecules with conjugated double bonds (e.g. benzene) but also to electron-rich ligands (e.g. acetate, sulfate, etc) and their metal complexes. These form the addresses in the nECM, which attract and bind the trace metal cations much like proteins and other electron-rich substrates do (c f., Lehninger, 2008; Eom and Song, 2019). As applied to the *tripartite* mechanism, "resonance" or "de-localization" means that the individual *cuinfo* is located in the nECM near a neuron (see Fig. 2), but that the related set of *cuinfo* constituting memory, are distributed in different anatomic compartments of the brain (Huk and Hart, 2019). The neural circuit consolidates these into a comprehensible pattern, ex-

perienced as memory. Thus, the engram is both local and "delocalized". That is, the basic memory units (*cuinfo*) are pixels that make up the pattern of memory are located near a specific neuron (see Fig. 2). But the set of *cuinfo* which make up the totality of the memory pattern is stored in different anatomic compartments of the brain. Thus, excising one particular region may not result in total memory loss or identify a specific locale where it is stored (see Lashley, 1950; Poznanski et al., 2019; Pribram and Meade, 1999).

Trace metals are quite reactive in terms of binding to electron-rich sites in proteins and GAGs and are critical for the activities of enzymes (Eom and Song, 2019). When released into the nECM, the metal cations interact with the electron-rich sites and help bind NTs to form relatively stable metal complexes (i.e. *cuinfo*), much like their complexation with enzymes (Warshel and Levitt, 1976). Some polyvalent metal complexes could also engage in redox (Fenton) reactions, with attendant covalent modifications involving new condensation or cross-linking reactions that further increase stability. For example, metals with multiple oxidation states (Al, Co, Cu, Fe , Mn), can engage in Fenton reactions to generate reactive hydroxyl (OH.) radicals (Kim et al., 2007; Wardman and Candeias, 1996). In turn, these oxidize and modify (tag and cross-link) the *cuinfo*. Thus, such reactions greatly enlarge the encoding repertoire available to the neuron and affect the content and stability of the derived *cuinfo* (Das et al., 2015; Marx and Gilon, 2013).

5. Concluding remark

We have identified NTs as the elicitors of physiologic responses entangled with emotive states, as the basis for a biochemical memory engram. In short, the *tripartite* mechanism provides a physiologically credible rationale for the phenomenon of emotive memory, consonant with the morphology of the neuron and the materials available to it.

Acknowledgment

We appreciate Randy Gallistel's remarks, which drew our attention to "memory" as the proper focus of our speculations. We also thank a reviewer for suggesting improvements and additional references.

Conflict of interest

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

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

Submitted: February 12, 2019
Accepted: June 10, 2019
Published: June 30, 2019

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