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Review Article

Interpreting Neural Morphology

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Abstract

From the time of Cajal, histologists, have attempted to understand how neurons encode memory. Cajal identified synaptic connections between neurons which Hebb conceptualized as "synaptic plasticity", processes related to recall. But aside from synaptic connectivity, they did not consider the "meaning" of the neuron's extended shape.

The neuron has a very large surface area with branching dendrites exposing surface spines that permit intimate exposure to the surroundings. Golgi perceived a perineural net (PNN) around the neuron, which Cajal dismissed as a "staining artifact". Subsequent work established the presence of a web of glycosamino-glycans and proteins around the neurons, termed extracellular matrix (nECM).

Recognizing that neural morphology and its interactions with its surroundings have functional relevance, we have proposed a tripartite mechanism of neural memory. It involves the chemical encoding of cognitive *units of information* (*cuin fo*), based on the interactions of three physiologic compartments, namely:

- Neurons – cells with large surface area, extended arborized shape with many dendrites.
- Extracellular matrix (nECM)- a static hydrogel, surrounding neurons.
- Dopants (trace metal cations and neurotransmitters (NTs)) – diffusible molecules which form which form metal-centered complexes within the nECM. The NTs are the molecular correlates of emotive states.

Thus, the nECM is not irrelevant but critical to the functioning of the arborized neuron. In conjunction with morphologic considerations, the tripartite mechanism permits one to construct a physiologically credible account for the encoding of neural memory.

Keywords: Neural Shape; Dendrites; Neurotransmitters; Neural Code; Trace Metals

Background

Cajal used Golgi's silver staining technique to visualize the slices of newborn chicks brains (Figure 1). Because the brains were not totally developed, he could identify individual neurons and was the first to describe the synaptic contacts between them.

Based on such observations, Cajal enunciated his principles of neural organization as follows:

- The individual signaling cell is a "neuron".
- Neurons communicate with one another not by direct contact, but by the signalling of axon of one to another's dendrite via a specialized regions called "synapses".
- Signaling is specific. A given neuron will only communicate with select neurons, not with all neighboring cells.
- Within a neuron, signals travel in only one direction.

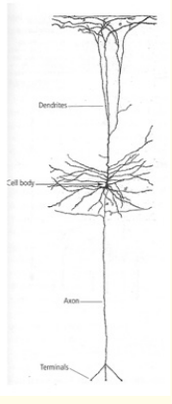

Figure 1: Cajal's drawing of a neuron [23,24]. Note that the neurons are represented as if suspended in space (i.e."naked"), absent a surrounding lattice of glycosminoglycans (GAGs) and proteins, altogether termed "extracellular matrix (nECM)".

Golgi, who invented the original silver stain histologic method, perceived a perineural net (PNN) around the neuron (now termed nECM), which Cajal and his followers generally ignored as a "staining artifact" [1,2].

Rather, Cajal enunciated the above principles of neural signaling and memory which involved exclusive synaptic contacts between neurons. Cajal's model of the "naked neuron" and of neural signaling was adopted by following generations of neuroscientists, notably by Hebb who enunciated the idea of "synaptic plasticity" to rationalize learning processes and memory [3-5].

Eventually (after 1950), the reality of the nECM was confirmed by biochemical analyses particularly periodate staining, electron microscopy (SEM, TEM) and other techniques [2,6-8]. However, few neuroscientists incorporated these findings into their concept of neural memory.

Thesis

Some have questioned whether Cajal's principles reflect the actuality of neural signalling [9-11]. Here, we examine whether neural morphology can be interpreted to clarify the processes underlying memory.

Form follows function

We accept that this architectural truism applies also to neurobiology. It has been posed: " why aren't all neurons spherical?" [12]. From a design perspective, the nuance of neural extended and arborized structure cannot be ignored. Just as it would be meaningless to describe a tree with roots and leaves, but without reference to soil or air, it is unseemly to ignore the neuron's splayed shape as it pertains to its signaling capabilities. In particular, one cannot ignore the surrounding extra-cellular -matrix (nECM) as irrelevant to the neuron's unique talents. Admittedly, the nECM performs "housekeeping" functions, permitting the diffusion of oxygen and nutrients into and waste out of the neurons [6,7,13]. But the nECM also performs a quite unique role which corresponds to neural shape, the encoding and storing of cognitive-information in the nECM, the basis of memory, as described by a tripartite mechanism.

Proposition: Tripartite mechanism of neural memory

The tripartite mechanism of neural memory [14-16]. involves the chemical encoding of cog-info based on the interactions of three physiologic compartments, namely:

- **Neurons** – spindly, multi-branched cells, synaptically and non-synaptically connected (electrically and chemically) to others. Modern studies have revealed that the neuron is a dynamic cell with malleable (plastic) synapses whose increased functionality are associated with learning and memory.
- **Matrix** – the neural extracellular matrix (nECM) surrounding the neurons. It comprises an anionic hydrogel of glycosaminoglycans (GAGs) and proteins, that permits the diffusion of small molecules and through which all signaling occurs.
- **Dopants** – diffusible metals + neurotransmitters (NTs) released from neural vesicles ...performing as chemical effectors of signals that encode cog-info within the nECM lattice.

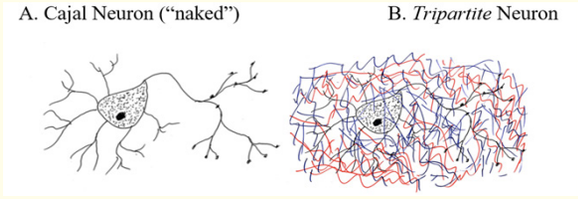

Figure 2: A. Drawing of an arborized neuron (a la Cajal) revealing many boutons (varicosities, spines) on its dendrites. Note absence of a background...as if the neuron were suspended in space i.e."naked". It was noted that most {>90%} of the neural dendrites do not make synaptic contact with another cell...they simply peter out into the nECM (adapted from [9]).

B. Corrected image, showing neuron with dendrites enmeshed in a surrounding nECM lattice.

The dendrites are covered with many spines emanting from their surface [12,17-19], which augment dendritic contact with the nECM and modulate memory recall.

A chemographic representation of the chemical process involving the neurons ejecting dopants into an anionic nECM "address" to encode cognitive information is presented in Figure 3.

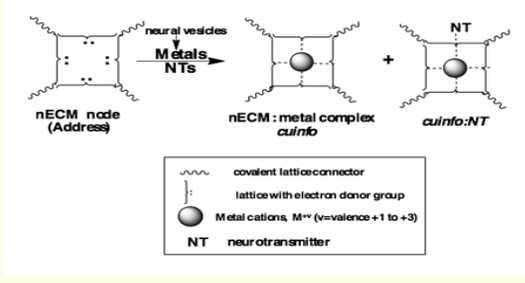

Figure 3: "Chemographic" representations of an electron-rich nECM "address" which becomes encoded as a cognitive unit of information (cuinfo - singular, plural) by binding a metal, as well as a neurotransmitter (NT).

Discussion

In keeping with the general principle: "Form follows function", we list particular points that reveal how the neuron's shape reflects its functions, as interpreted through the tripartite mechanism as follows:

1. Neuron's highly extended structure with large surface area indicate intimate contact with its surroundings [20,21]. Membrane surface area of neuron = 250,000 um2
2. Presence of nECM around neurons (many refs).
3. Most neural dendrites do not establish synaptic contacts, but simply extend into the nECM.
4. The aquisition of trace metal cations and neurotransmitters (NTs) into neural vesicles, which are released into the nECM upon neuron activation [22-26].
5. The critical role of dendritic spines in neural signalling. These may change shape following a learning experience.

Conclusion

The neuron's shape speaks volumes about its potential signaling modalities.

Neural shape can:

- Effect synaptic, electrodynamic signaling along its longitudinal axis through its axon.
- Enable lateral chemodynamic signaling via dendrites enmeshed in the nECM.

Morphology morphs into "meaning".

Clearly, neural shape reveals its proclivity to interact with its surrounding nECM. Recognition of this functional aspect of neural morphology will help neuroscientists comprehend the heretofore ignored biochemical processes involved in the formation of memory.

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

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

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