Review Article

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Connectome Projects and Mentality

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ABSTRACT

The various Connectome Projects were undertaken to clarify how the brain works by detailing neural ultrastructures in the brains of c. elgans, mouse and humans.

The stated aims of the Connectome projects are:

a. To unravel the synaptic-scale organization of the brain.
b. To chart the circuits that coordinate the brain's many functions.
c. To understand fundamental cognitive operations

A review by Eisenstein of these Connectomic Collaborations discussed the results. But this review was somewhat lacking in critical perspective, as will be elaborated below.

The Connectome groups as well as Eisenstein review failed to point to the overlooked aspects of neural structure, namely, the neural extracellular matrix hydrogel (nECM/PNN) surrounding all neurons. The presence of nECM/PNN was confirmed by alternate staining techniques, by electron microscopy (TEM, SEM) and mass spectrometry. Thus, there are no " naked " neurons. However, few neuroscientists incorporated these findings into their evaluation of neural connectivity or mental talent.

We have previously proposed a tripartite mechanism of neural memory based on a biochemical mechanism, where cognitive unit of information (cuinfo) are realized as metal-centered complexes in the nECM/PNN. The cuinfo code permits the encoding of emotive states by complexing neurotransmitters (NTs) released by neurons/glial cells. Thus, we summarize the facts and hypothesize an operative process.

The myopia of the Connectome group and the reviewer blinded them to the totality of neural ultrastructure which includes nECM/PNN and rendered them incapable of formulating a credible mechanism of brain mentality, though they did admit that "the more we know (about structure), the harder it is to turn this into an easy-to-understand model".

Keywords

nECM, PNN, Cognitive information, Neurotransmitters, Tripartite, Memory, Mentality.

Background

The Ultimate Aim of Neuroscience is to Understand the Workings of the Human Brain

How does the brain transform caloric energy into mentality experienced as memory, emotions and consciousness? Clearly the brain engages in the many metabolic processes characteristic of all other cellular organs (liver, kidney, lungs, etc.). They involve blood flow, diffusion of metabolites, oxygenation, caloric cycles, etc. The goal of modern neurobiologists is to comprehend the unique workings of the brain that generate mental states. To that end, we looked at old and new publications for mechanistic revelations but only found vague, philosophically inclined discussions [1-6]. More to the point, the modern works focused on metabolic details or genomic trails (see May 24, 2024 issue of Science "Decoding the Brain"). But they avoided grappling with the transformation of metabolic energy into a mental state or the subject of mentality (i.e. consciousness), attendant with emotions and memory.

We were encouraged when we became aware of the work of various neurobiology groups working under the rubric of Connectome, some of which we cite here [7-16]. Though we searched all the cited references, we found no match for words relating to mental functionality i.e. memory, emotions, consciousness. The phrases employed in these Connectome publications were: " informative structural properties", "generative computational models", "hypotheses of synaptic connectivity", "defining how information flows through such a complex system", "understanding of the structure and function of the neuronal connectome", "directly involved in aspects of mamalian behavior". They comingled the meanings of "signaling" and "information". In effect, they tip-toed around mentality by adopting allegorical phrasing. Curiously, the term "mental" was generally part of another word i.e.

Mentioning "Mental"

Experi-mental
Funda-mental
Ele-mental
Eviron-mental
Develop-mental
Monu-mental
Detri-mental

Definition

Connectome is the complete point -to-point structural connectivity of neural pathways in the brain (Toga).

Goals

The stated aims of the Connectome projects are

a. To unravel the synaptic-scale organization of the brain.
b. To chart the circuits that coordinate the brain's many functions.
c. To understand fundamental cognitive operations.

The various Connectome Projects were undertaken to clarify how the brain works by clarifying neural ultrastructures in the brains of *c. elgans*, mouse and human. Longstanding wisdom about neural nets is that they are exclusively connected via synaptic gaps. This was the model first proposed by Cajal and is now referred to as the "neuronal doctrine" [17-19]. Golgi, the inventor of the silver stain method used by Cajal, disagreed. He proposed that the nervous system is a syncytial continuum with neurons signaling through shared membranes. Moreover, Golgi perceived a perineural net (PNN) around the neurons, which Cajal dismissed as a staining artifact. To this day, most neuroscience texbooks represent neurons "a la Cajal," as if they were suspended in space, i.e. "naked". They do not refer to the web of glycosaminoglycans (GAGs) that surround all neurons. The Connectome Projects continue this Cajalian tradition, though with much greater ultrastructural detail.

Evolution

The Connectome Projects employed a number of techniques to characterize mouse and human brains by various techniques: electrophysiology, electron microscopy and fMRI, EEG to detect signaling between neurons and to identify neural circuits [7-16]. Fluorescnce microscopy was employed to detect active neurons. Thus, the Connectome groups have generated unprecedented detailed structural images of neural circuits in a small volume of the mouse brain. A review by Eisenstein [20] of these Connectomic Collaborations discussed the results achieved by the analysis of 1 cubic mm (i.e. 0.2%) of a mouse brain by a combination of 3D electron microscopy (EM) and fluorescent imaging of neuronal activity from the same volume. But this review was somewhat lacking in critical perspective, as will be elaborated below.

In that the brain is physiologic organ that operates under the same conditions as all other body parts (lungs, kidneys, eyes, etc.), one would expect that a mechanistic description of the brain's unique process of consciousness would be couched in terms related to the evolution of biochemical signaling processes undergone by all the other creatures.

We are encouraged in this view as memory is a talent that can be traced back to the signaling of bacterial colonies [17-21]. They employ molecular modulators (i.e. cationic metals, biogenic amines, amino acids, acetylcholine and NO) to signal positive or negative responses to external stimuli.

Evolving neural creatures developed new signaling molecules in addition to the bacterial signaling modulators, now termed “neurotransmitters” (NTs), all which elicit physiologic reactions termed “feelings” as well as psychic (emotive) reactions. Conscious mental states (i.e. emotions) are inextricably linked (entangled) with the memory of physiologic responses instigated by the NTs.

The primitive worm *c. elegans* with 302 neurons has demonstrable memory and it employs the same repertoire of signaling molecules as bacteria [22,23]. Thus, one could posit that bacteria and *c. elegans* are demonstrably endowed with a memory function analogous to that of bacteria signaling. And so on up the evolutionary ladder (Table 1).

The question of whether neural connectivity defines consciousness or mental state is an intricate topic with ongoing debates among neuroscientists, cognitive scientists, and philosophers. While connectivity plays a significant role, it's not the sole defining factor. Below is an overview of various theories and empirical studies that indicate the relationship between connectivity and consciousness (Table 1).

Facts

One craves a fuller concept of mentality than offered by a catalogue of ultrastructural connections. The Connectome groups as well as Eisenstein's review failed to point to the overlooked aspects of neural organization, namely, the neural extracellular matrix (nECM/PNN) surrounding all neurons. That is, Golgi's silver stain beautifully visualizes neural membranes [18-20]. However, it does not detect the glycosaminoglycans (GAG) surrounding the neurons.

The term "nECM/PNN" typically refers to the neuronal

extracellular matrix (nECM) and Perineuronal Nets (PNNs), which are specialized structures within the brain's extracellular matrix known to play important roles in neural development, synaptic plasticity, and neuroprotection. The existence of nECM and PNNs is well-documented through a variety of experimental proofs, including (Table 2).

Behavioral and memory loss correlated with degradation of PNNs. Similarly, alterations in PNNs and nECM are often associated with memory loss following traumatic brain injuries or neurodegenerative conditions.

Table 1: Defining Neurologic Consciousness.

1. Neural Connectivity and Consciousness:

A. Refers to the physical arrangement of neural pathways and synapses.

Techniques such as diffusion tensor imaging (DTI) allow mapping of brain networks, aiding in comprehending the "connectome" [13].

B. Involves analyzing temporal correlations between neural activities across different brain regions, measured commonly via functional MRI (fMRI) [2].

It's concerned with dynamic interactions and synchronization of neural populations.

2. Theories of Consciousness

A. Integrated Information Theory (IIT): IT postulates that consciousness amounts to the integration of information across a system. Higher degrees of integrated information are hypothesized to indicate more potent conscious experiences [11,14].

B. Global Workspace Theory (GWT): Suggests consciousness arises when information is widely broadcast across the brain's "global workspace," allowing integration of activity across disparate neural systems [1].

C. Recurrent Processing Theory (RPT): Emphasizes the role of recurrent (feedback) neural activity. As opposed to feedfor-ward processing, recurrent interactions are crucial for generating conscious experiences [8].

3. Empirical Evidence

A. Disorders of Consciousness: Studies on patients with conditions like vegetative state, minimally conscious state, and locked-in syndrome show a strong correlation between altered structural and functional connectivity and levels of consciousness [9].

B. Altered States of Consciousness: Functional connectivity changes associated with different states such as sleep, anesthesia, or psychedelic experiences indicate altered connectivity patterns correlating with shifts in consciousness [4,5].

Table 2: Experimental proofs for the presence of nECM/PNN [21-27].

1. Wisteria floribunda agglutinin (WFA) Staining: This specific lectin binds to N- acetylgalactosamine, a sugar moiety found on proteoglycans in PNNs [15].

2. Hyaluronic Acid: Can be visualized using specific dye stains or molecular markers [16].

3. Antibodies Against Chondroitin Sulfate Proteoglycans (CSPGs): Such as aggrecan, neurocan, versican, and brevican, key components of PNNs and nECM that can be visualized using specific antibodies [17].

4. Antibodies Against Link Proteins: Such as tenascin and hyaluronan and proteoglycan link protein 1 (HAPLN1) which bind to CSPGs and hyaluronic acid, helping establish the mesh-like structures characteristic of PNNs [18].

5. Confocal Microscopy: This high-resolution imaging technique allows for detailed visualization of PNNs and nECM in tissue samples [19].

6. Electron Microscopy (TEM, SEM): Provides ultrastructural details at the nanoscale level, revealing the intricate organization of PNNs and the nECM [20].

7. RT-PCR and in Situ Hybridization: Detect the mRNA expression levels of genes encoding ECM components like aggrecan, hyaluronic acid synthases, and other proteins [21].

8. Single-cell Transcriptomics: Evinces the specific ECM-related gene expression profile of individual neurons and glial cells [22].

9. Western Blotting: Detect specific ECM proteins from electrophoresis of tissue extracts [23].

10. Mass Spectrometry: Can identify and quantify numerous ECM components, providing a broad overview of the ECM's molecular composition [24].

11. Enzyme Digestion: Chondroitinase ABC can be used to specifically degrade PNNs. Provides functional evidence of PNN existence and roles [25].

12. Knockout/Knockdown Studies: Genetic techniques to remove or reduce the expression of specific ECM components to reveal their functional importance *in vivo* [26].

13. Two-Photon Microscopy: Suitable for visualizing ECM structures in living animals, especially in combination with genetically encoded fluorescent markers or dyes [27].

Thus, there are no "naked" neurons. All are cocooned in a nECM/PNN hydrogel which has many metabolic functions related to cell viability, such as diffusions of oxygen and metabolites. Astrocytes are also intimately associated with synapses and are involved in depositing the PNN molecular scaffold deposited in the interface between the astrocyte and neurons [28-31]. Moreover, histologic observations indicated that most neural dendritic extensions are not engaged in synaptic contact with others. Rather, they peter out into the surrounding nECM [32-41]. Thus, one should consider both synaptic and ephaptic modes of neural signaling. However, few neuroscientists incorporated these findings in their models of consciousness.

Mentality

We have proposed that the nECM/PNN functions as a "memory material" [42] wherein cognitive information is encoded with metal cations and neurotransmitters (NTs) ejected by the neurons (see tripartite mechanism of neural memory, [72-83]). All the more reason to consider the nECM/PNN when discussing the ultrastructure and functions of neural nets.

The Consortium groups as well as Eisenstein's review, do not address the core enigma of brain activity, the mechanism of mentation. Though it is the crux of our interest in brain activity, the Connectome group does not mention psychic phenomena or cast a critical eye over the structural details they provide. Eisenstein's review also does not identify deficiencies [20]. He performs as a cheer-leader for the teams, but does not consider the wider context of the structure or point to deficiencies in reportage.

The neuroscience community has been grappling with the enigma of brain function for many years. How does the brain generate mental states? What is the source of consciousness? What is the mechanism of memory [1-6,35]? Can it be ascribed to the evolution of signaling processes in evolving creatures? Responsible reportage in social media as well as neuroscience journals should provide historically informed interpretations of experimental findings (facts) as relating thereto.

Tripartite Mechanism of Emotive Memory

We have previously proposed that neural memory is based on a biochemical mechanism, where cognitive unit of information *(cuinfo)* are realized materially as metal centered complexes in the nECM. The *cuinfo* code permits the encoding of emotive states by complexing neurotransmitters (NTs) released by neurons/glial cells [72-83]. Incoming perceptions are encoded with trace metals + neurotransmitters (NTs) to form metal-centered *cuinfo*. We have developed a chemographic notation for the tripartite mechanism which captures the essence of this regarding emotive memory (Figures 1, 2).

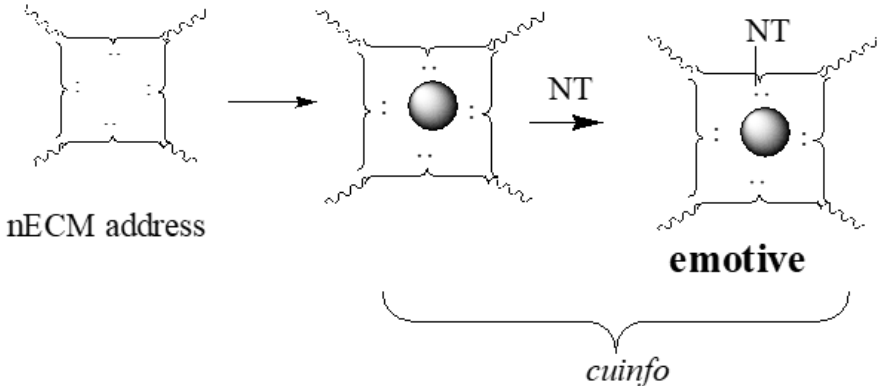

Figure 1: Tripartite chemographic representations of cognitive units of information (*cuinfo*) by which neural memory is stored and reconstructed.

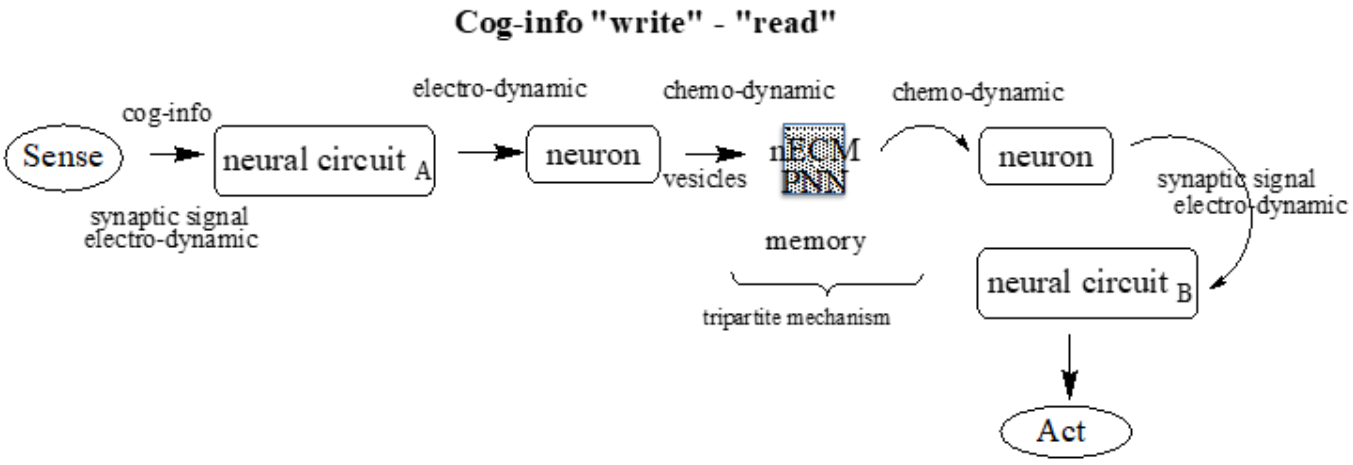

Figure 2: Schematic of the process whereby cognitive information (cog-info) is processed (written) into nECM memory, then chemo-dynamically "read" by the neural circuit (tripartite mechanism), consolidated into conscious memory to be acted upon.

Facts and Hypothesis

An update on major projects such as the Connectome should report experimental findings and place them in a biologically credible context. Reviewers should point out factual deficiencies that might distort the meaning of reported findings.

Facts which support the proposed tripartite mechanism of memory are:

1. Neural Morphology - splayed shape with large surface exposure to the surrounding matrix. Most dendrites do not establish a synaptic contact with neighboring neurons, but simply terminate in the surrounding matrix [41,42].
2. nECM/PNN, a hydrogel of glycosaminoglycans that surrounds all neurons (Table 2) [28-38]. It has been suggested that it performs as a "memory material".
3. Signaling- the neuron employs two modes of signaling, via the synaptic gap mode, as visualized by Cajal and all following neuroscientists; the ephaptic mode, a chemical signaling process by ejecting vesicles containing metal cations and neurotransmitters (NTs) through the exposed membrane (not easily visualized).
4. Trace metals in the brain as detected by atomic absorption, mass spectrometry and neutron activation analysis (AA, LS-MS, NAA) (many refs). Mental effects of trace metal deficiency or toxicity on mood and memory is well documented [51,52].
5. Effects of neurotransmitters (NTs) on both physiologic reactions and mental states.
6. The conservation of signaling molecules from bacteria on upward to evolved primates. All employ the bacterial repertoire of core signaling molecules, somewhat augmented by more evolved creatures.

Thus we posit that neurons are surrounded by nECM/PNN, which performs as a neurochemical “memory material” wherein units of memory are encoded as cognitive units of information (*cuinfo*) and decoded by the neural circuits as emotive memory [72-83]. This tripartite mechanism is consonant with experimental observations (i.e. facts) as they relate to neural ultrastructure and interactions with the surrounding matrix (i.e. via synaptic as well as non-synaptic, ephaptic signaling). This mechanism involves only materials available to neurons (i.e. nECM/PNN, trace metals, NTs).

Chemistry

As with all descriptions of biologic function, it is the discipline of chemistry that provides a vocabulary and process concepts (mechanisms) that applies to the evolution and operation of mental states. In that mentality expressed as memory is based on neural signaling, it is worthwhile to consider the origins of biologic signaling and its constituent components.

For example, bacteria respond to the environment by signaling with small molecules termed "biomodulators", comprised of biogenic amines and amino acids. The evolved neurons adopted the same modulators, as well as with additional neuropeptides now termed " neurotransmitters" (NTs), to signal one another. These are critical components that permit neural nets to achieve mental states.

Maps

Ultrastructural studies by themselves cannot be expected to pierce the veil of the brain's psychic talents expressed as memory and emotions. For example, if one were to be given a map of the London underground, that would not divulge how it works. One would need to know how many trains, their schedules, their routes, the transfer points and comprehend all the track signals.

The myopia of the Connectome group and the reviewer blinded them to the totality of neural function. They overlooked a critical component not visualized by their mapping techniques. Thus, they ignored the literature which described the nECM/PNN in detail (Table 2). Their conceptual "blind spot" rendered them incapable of formulating a credible mechanism of brain mentality which they ignored, though they did admit that "*the more we know (about structure), the harder it is to turn this into an easy-to-understand model*".

The experience of mentality raises many questions relating to process. What are its biological roots and how did it evolve? It does not fall into the category of observable physical forces i.e. Gravity, electromagnetism, weak and strong nuclear attractions. If not in spacetime, in what dimension is it expressed?

The enigmas of memory and consciousness continue to haunt the dreams of cognitive scientists. We continue to confront these enigmas by focusing on molecular mechanisms. In particular, we consider how psychic states can be biochemically encoded in conscious memory.

Future Experimental Directions

We suggest the following experiments to clarify the phenomena of mentality, as follows:

1. Analyze and compare the nECM/PNN extracted from different anatomic regions of the brain (i.e. amygdala, hippocanpus, visual cortex, etc.).
2. Establish cell cultures of neurons/glial cells. Analyze the nECM they generate.
3. Evaluate the electrical and chemical responses of such cell cultures to applied neurotransmitters (i.e. dopamine, epinephrine, etc.).
4. Monitor the responses of impedimetric electrodes coated with polysaccharide analogues of nECM to different metals. This would be a continuation of work already published [53,54].

Mentality is unique natural force. It requires metabolic energy but escapes the grasp of classical quantum thermodynamics. One is a loss to describe the thermodymamic conversion of caloric energy into emotive mentality.

The metrics of emotive states cannot be captured by maps, numbers or even by words. In spite of the computer scientists mis-appropriation of terms such as "*neural net*" and "*deep neural learning*", they throw little light on biological neural processes

that evoke memory and emotions. Such verbal prestidigitations mix up attempts to comprehend how biological neural nets operate to generate mental states. It seems that a new paradigm must be adopted to address the emergence of mental states from the biochemical workings of neural nets. We really have to think "outside the box". Hopefully, an emergent account might explain how the biochemistry of complex organisms links the physical with the mental.

Analogous to physicists' inability to penetrate processes occurring in "black holes" or to clarify "dark matter", neuroscientists may not be able to describe the processes that enable neural nets to generate mental states. The synaptic and non-synaptic signaling processes might be the "*neural event horizon*" beyond the ken of language and logic. Like the physicists' inability to approach a black hole beyond its *"event horizon*" [55], the neuroscientist too may not be able to render a rational description of the emotive states experienced and recalled by neural nets.

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