

The Interactome Hypothesis of Depression

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Abstract

It has long been known that the most important function of platelets is to stop the flow of blood from wounds with the help of a set of enzymes, proteins, and lipids supporting complex metabolic clot-forming mechanisms. It is also known that there are close correlations, both enzymatic and metabolic, between platelets and nerve cells with respect to the metabolism of several neurotransmitters such as serotonin, dopamine, GABA, etc. Platelets, which serve an historic role as biological markers in psychiatry, can in fact be regarded as virtual "circulating neurons" or "brain ambassadors" that may offer a significant advantage in understanding the neurophysiology of psychiatric disorders including depression. Critical points of potential specific linkage between platelets and depression include serotonin and membrane platelet fatty acids in relation to the cytoskeletal quantum-nanowire network. This paper advances an "interactome" hypothesis of possible connections among enterochromaffin cells, serotonin, platelets and cytoskeletal proteins related to brain neurons with implications regarding the genesis of depressive psychopathology.

Key Words: brain neurons, serotonin, enterochromaffin cells, platelets, fatty acids, cytoskeletal proteins, modified membrane fluidity, arachidonic acid, post-synaptic density interactome, cytoskeletal quantum-nanowire network

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Introduction

The main focus of the present article is a discussion of various neuro-chemical pathways that may underlie psychiatric disorders, particularly depression. An important aspect of the model described is a link between the quantum and the molecular domains involved in depression.

1. Recent Advances in Depression

Major depression (MD) is a common psychiatric disorder with a complex and multifactorial aetiology. Potential mechanisms associated with the pathogenesis of this disorder include monoamine deficits, hypothalamic-pituitary-adrenal axis dysfunction, inflammatory processes, and/or neurodegenerative alterations (Zunszain, 2010). Depression is highly prevalent in infectious, autoimmune, and neurodegenerative diseases and, at the same time, depressed patients show higher levels of pro-inflammatory cytokines (Wichers, 2002). In 2008 Maes showed that intestinal mucosal dysfunction, involving an increased translocation of gram-negative bacteria (leaky gut), plays an inflammatory role in the pathophysiology of depression. It is suggested that the increased

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lipopolysaccharide translocation may mount an immune response of cytokines and thus inflammatory activation in some patients with major depression (Maes, 2008).

One of the mechanisms by which chronic inflammation might trigger and/or maintain the development of depression is transcriptional induction of indoleamine 2, 3-dioxygenase (IDO), the rate-limiting enzyme of the tryptophan (TRY)-kynurenine pathway, by pro-inflammatory cytokines. Activation of IDO shifts TRY metabolism from serotonin synthesis to formation of "kynurenines." Diminished serotonin production has a well established association with depressed mood, while increased formation of kynurenines might contribute to development of late-onset depression via their apoptotic, neurotoxic, and oxidative effects and through up-regulation of inducible nitric oxide synthase, phospholipase A₂, arachidonic acid, prostaglandin, 5-lipoxygenase, and leukotriene cascades (Oxenkrug, 2010). Recent work, focusing on the relationships between serotonin and bone formation, covers the main steps of the above-mentioned serotonin pathway from enterochromaffin cells to platelets, reprising its complex physiology encompassing synthesis, transport, reuptake, and receptor activation. Rosen argues that, in the brain, alterations of 5-HTT (hydroxytryptophan transporter), which induces reuptake of serotonin, may be the functional locus of responsibility for affective disorders including depression (Rosen, 2009; Gershon, 2007).

2. A Molecular Hypothesis of Depression

2.1 Arachidonic Acid, Membrane Fluidity and Serotonin

Arachidonic acid (AA) is a 20-carbon ω -6 essential fatty acid (Cunnane, 2003). Most AA in the human body is derived from dietary linoleic acid (another essential fatty acid) which comes both from vegetable oils and animal fats. AA is one of the most abundant fatty acids in the brain (approximately 10% of its fatty acid content) (Crawford, 1972). It sits at the head of the "arachidonic acid cascade" composed of more than twenty different signalling paths that control a wide array of bodily functions, especially those involving inflammation and

the central nervous system. The AA acid cascade is arguably the most elaborate signaling system known to neurobiologists (Piomelli, 2000). Neurological health is reliant upon sufficient levels of arachidonic acid. Among other things, AA helps to maintain hippocampal cell membrane fluidity (Fukaya, 2007). AA also helps to protect the brain from oxidative stress by activating peroxisomal proliferator-activated receptor- γ (Wang, 2006). In addition, AA activates syntaxin-3, a protein involved in the growth and repair of neurons (Darios, 2006). Green et al, with specific relevance to the present paper's focus on the neurobiology of depressed mood, demonstrated that brains from rats with depression have high concentrations of AA (Green, 2005).

Neurons can take up preformed AA, but they cannot synthesize it *de novo* as other cells do by elongation and desaturation of dietary linoleic acid. The liver is a major AA source for neurons via the somatic circulatory system, but two non-neural types of cells, cerebral endothelium and astrocytes, within the CNS also appear to play an important role. These cells accumulate circulating linoleate, use it to synthesize AA, and secrete the latter into the interstitial medium, making it available to neurons. Neurons take up free AA from the interstitium and store it rapidly by esterifying it to membrane phospholipids. As a result, only trace levels of free arachidonate may be found in resting cells. Some recent papers dealing with quantitative aspects of human depression have tried to explain the possible role of platelet membrane viscosity in modulating brain serotonin through a process which involves AA. Originally, it had been shown that principally three fatty acids are involved in platelet biochemical characterization of depression; these three fatty acids are palmitic acid (PA), linoleic acid (LA) and AA (Cocchi, 2008). The platelet membrane was found to display a greater degree of desaturation in depressed humans compared to a group of clinically healthy subjects, and there emerged a direct relationship of the AA level with reference to platelet and brain and an inverse relationship regarding serotonin (Cocchi, 2009a, b; Tonello, 2010; Cocchi, 2010a, b).

2.2 Serotonin in Enterochromaffin Cells and Platelets

Enterochromaffin cells (EC) are endocrine cells located in the epithelia lining the lumens of the intestinal and respiratory tracts. They produce and contain about 90% of the body's store of serotonin (5-HT). Their distribution throughout the intestinal mucosa makes them suitable to function as biomolecular transducers of information between the intestinal lumen and the nervous system. EC secrete serotonin, corticotrophin-releasing hormone, cholecystokinin, and somatostatin in response to luminal triggers such as microbial factors (from the microbioma) and central stimuli. Serotonin appears to be a central physiological mediator of the brain-gut connection (Rhee, 2009).

Serotonin is present at high concentration in platelets, where it is accumulated from the plasma by the selective reuptake transporter (SERT). SERT systems are present also in EC and enteric neurons (EN). In blood more than 95% of serotonin is stored in platelets, which become loaded with serotonin as they pass through the intestinal circulation (Lesurtel, 2008).

The pioneering work of Boullin and O'Brien discusses a large reduction of endogenous platelet 5-HT reported in individuals with trisomy 21. The reduced platelet 5-HT concentrations found in Down's syndrome may be due to an abnormal uptake mechanism plus excessive efflux resulting from shortage of ATP. Other possible contributory causes with regard to the low platelet serotonin content are defective synthesis by enterochromaffin cells in the gastro-intestinal mucosa and increased metabolism by platelet monoamine oxidase. (Boullin, 1971). Several authors have observed that in the blood of patients with Down's syndrome 5-HT is reduced (Rosner, 1965; Tu, 1965; Jerome, 1967) because of a possible defect in serotonin transport and have suggested that, if platelets are a valid model for serotonergic neurons, any changes observed in platelets should imply similar possible effects within the brain. However, low concentration of serotonin in both platelets and neurons, widely described among depressed patients, fail to explain the

specific relationship between platelets and neurons in depression, insofar as serotonin does not cross the blood brain barrier. (Takahashi, 1976; Kim, 1982; Dreux, 1985; Camacho, 2000; Plein, 2001). Instead, some results suggest another relationship through the mediation of AA for two main reasons:

1. When platelets are saturated with AA, they are unable to transfer and receive AA from neurons and hence AA increases in the brain, reducing membrane viscosity (increasing fluidity) (Cocchi, 2009, 2010c).
2. According to Heron the accessibility of serotonin to receptors decreases with membrane fluidity (increases with membrane viscosity) (Heron, 1980).

The *de facto* link between platelets and neurons can be conceived as membrane AA concentration that determines higher or lower viscosity of the membrane and this link seems to explain observed similarities between neurons and platelets in depression (Tonello, 2010; Cocchi, 2010a, b).

3. The Post-Synaptic Density Interactome

Cellular systems rely on multiprotein complexes in which individual proteins associate into functional modules. Many gene products mediate their function within macromolecular networks configured by topological and dynamical properties that reflect biological phenomena. Understanding of biological and pathogenetic processes requires a comprehensive study of the structure, function, and dynamics of networks within and among macromolecular systems (Alberts, 1998; Hartwell, 1999; Jeong, 2001; Han, 2004). Such understanding spans sub-domains including membrane-related fatty acids; serotonin and its affiliated brain, gut, and platelet apparatus; cytoskeletal quantum-nanowires subserving qualitative and potentially mood-relevant aspects of consciousness; and the larger ambient microbiome-inclusive biosphere in which all of these sub-domains are embedded.

The interactome can be defined "*as the whole [array of] molecular interactions that take place in an organism and allow the cascade of regulatory molecules including the mechanism of action of enzymes and*

metabolic reactions.” The interactions between different proteins in fact constitute those basic physiological mechanisms that regulate and monitor the performance of all bodily functions. Decomposition of the overall protein interaction network reveals functional modules and motifs (Rual, 2005). Recent data estimate approximately 650,000 interactions among human proteins (Stumpf, 2008).

An average human body is made of about 10^{13} cells. The number of micro-organisms which inhabit an adult human body is estimated to be about 10^{14} cells. This means that 90% of our body is non-human. Bacterial communities surround us and give us support, so that we are intimately connected with them. In fact, many basic human processes depend crucially on the trillions of microbes which immediately following birth start to colonize our bodies. The vast majority of these micro-organisms are not dangerous; on the contrary, they provide some basic functions, for example helping to digest food, to break down toxins, and to fight diseases caused by other invading microbes. The microbiome comprises the complete collection of microbes (bacteria, fungi, viruses, etc.) that co-exist naturally in the human body. The “human biosphere” is the sum of all non-human (microbiome) and human cells occupying the space of our physical body. In the new model developed by us, the interactome encompasses the interactions between proteins simultaneously with all other physical and chemical interactions taking place in the human biosphere.

3.1 The G α Protein

The seven recognized families of serotonin receptors are termed 5-HT₁ through 5-HT₇. With the exception of the 5-HT₃ receptor, a ligand-gated ion channel, all other serotonin receptors are G protein-coupled receptors that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response. Receptors 5-HT_{1A} to 5-HT_{1F} are coupled to the protein G_i, which inhibits the cAMP-dependent pathway by suppressing production of cAMP from ATP. Receptors 5-HT_{2A} to 5-HT_{2C} are coupled to protein G_{q/11 α} , stimulating membrane-bound phospholipase C, which then cleaves PIP₂ (a minor membrane phosphoinositol)

into two second messengers, IP₃ and diacylglycerol. Receptors 5-HT₄ to 5-HT₇ are coupled to protein G α , which enhances the production of cAMP from ATP via direct stimulation of the membrane-associated enzyme adenylate cyclase; cAMP acts as a second messenger that goes on to interact with and activate protein kinase A, which can then phosphorylate myriad downstream targets.

Lipid rafts are specialised structures on the plasma membrane that have an altered lipid composition as well as links to the cytoskeleton. S-palmitoylation is the covalent attachment of fatty acids, such as palmitic acid, to cysteine residues of membrane proteins including G α . Signal transduction, either through activation of adenylate cyclase by the ligand-receptor complex or through micro-aggregation of ligand-receptor complexes, is associated with membrane components’ lateral movements, determined at least partially by lipid fluidity (Popova, 2002). Rasenick’s research group, studying the G α protein’s potentially pathogenetic role in risks for suicide, has focused on the membrane lipid raft microdomain as the critical element of neuronal vulnerability shaping a possible etiological route to depression. Recent findings show that a molecular circuit, originating in membrane viscosity, can modulate the molecular cascade involving G α protein and tubulin (Cocchi, 2010a, b; Donati, 2008).

3.2 The G α Protein - Tubulin Interaction

Microtubules (MTs) and actin filaments are the primary interacting partners of lipid rafts. The building block of MTs is tubulin, a 110-kDa heterodimeric protein that is the association product of two different subunits, designated α and β tubulin. Each tubulin heterodimer binds two molecules of guanine nucleoside phosphate (GTP) and exhibits GTPase activity closely linked to assembly and disassembly of MTs. Outside MTs, tubulin is anchored to the lipid raft of the plasma membrane. It is known that G α protein interacts with tubulin, promoting its GTPase activity and increasing the dynamic behavior of MTs (Wang, 1991; Layden, 2008). In the case of 5-HT receptors

coupled to protein Gq/11 α , signal transduction is activated by tubulin through a direct transfer of GTP from tubulin to Gq/11 α (Popova, 2002).

Over the course of the last decade many theories and papers have been published concerning the biophysical properties of MTs, including the hypothesis of MTs as substrates of coherent quantum states evolving superpositional information and energy transfer over time in relationship to consciousness-supporting processes in the brain. The post-synaptic density may be considered as the site of an interactome whose main protein interaction is between G α and tubulin, this protein-protein interaction alteration sitting at a crossroad of

the molecular and quantum phenomena potentially implicated in conscious aspects of depressive psychopathology. A plausible path linking serotonin transfer between EC and platelets to the interactome connection under conditions of euthymia (Figure 1) and depression (Figure 2) according to experimental findings (Cocchi, 2008, 2010a,b; Donati, 2008) thus has possible resonances within the quantum domain (Hameroff, 1996, 2009). The effects of these altered interactions could influence dramatically states of consciousness by disrupting the regular features of cellular automata operating through the cytoskeletal quantum-nanowire network.

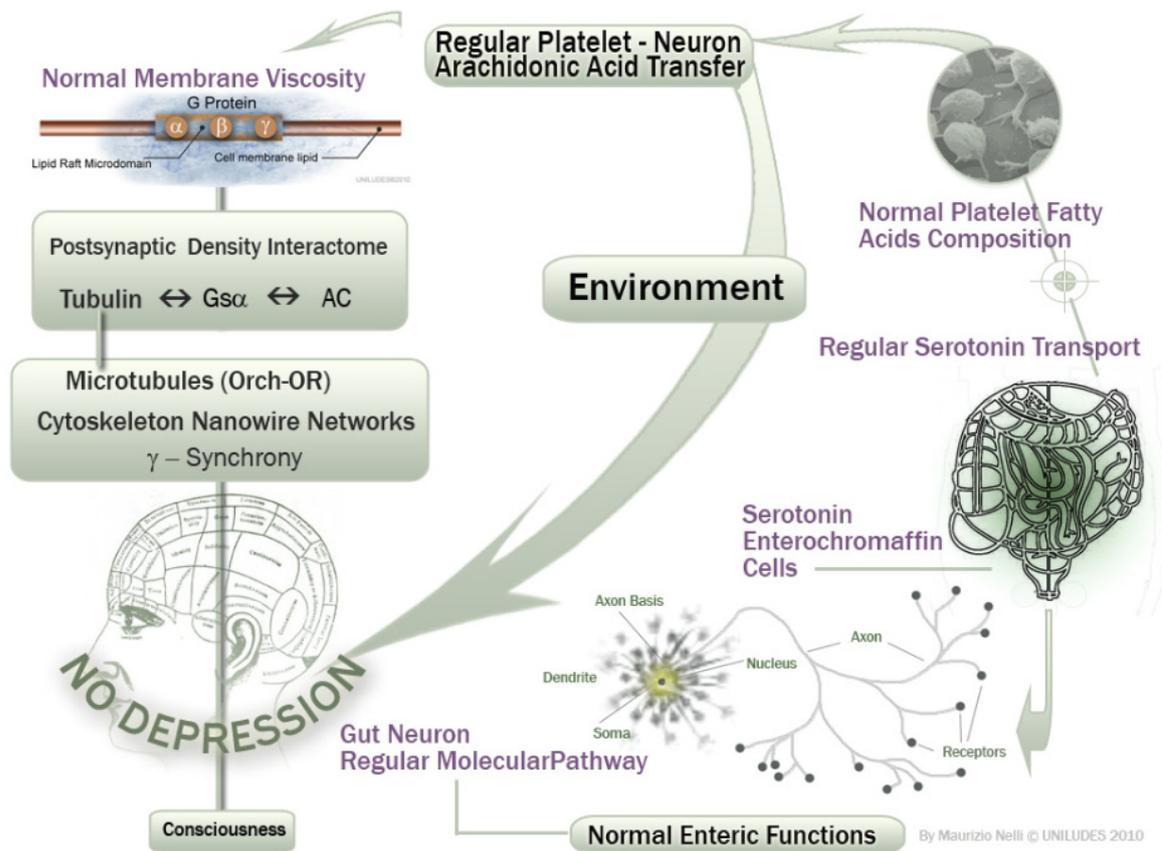


Figure 1. Figure shows a schematic description of the serotonin pathway from enterochromaffin cells (EC) to platelets and interactome regulation through membrane viscosity under normal conditions.

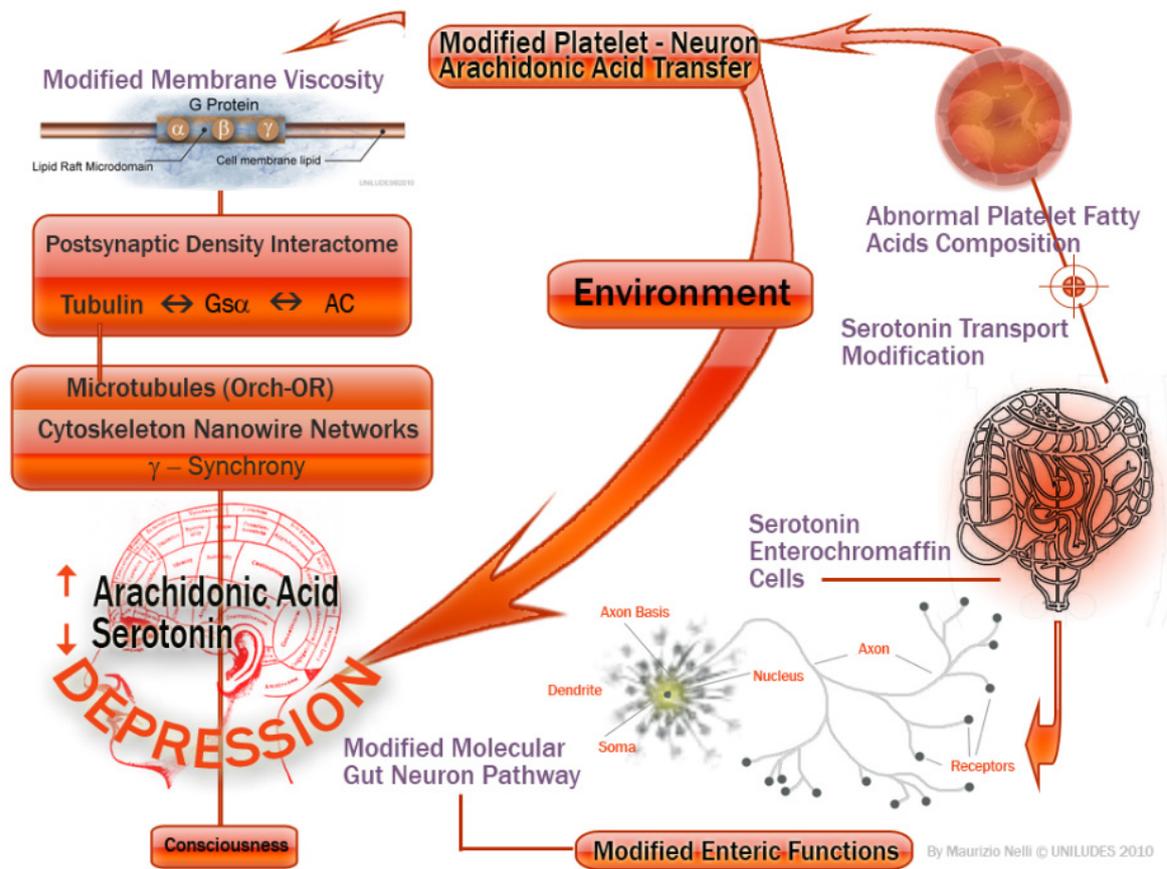


Figure 2. Figure shows a schematic depiction of the serotonin pathway from EC to platelets and regulation of the interactome through membrane viscosity under conditions of platelet membrane fatty acid modification.

4. The Cytoskeletal Quantum-Nanowire Network

MTs and actin filaments can be viewed as computationally relevant nanowire networks that within neurons provide several functions, among them connection of the cell nucleus with the postsynaptic density (Woolf, 2010). Potential computational modes for MTs and actin filaments are beginning to be understood, with two main quantum models for MT information processing having been proposed. One recent quantum MT model, advanced by Craddock and Tuszynski, describes classical and quantum information processing mediated by a double-well potential within the interior of the tubulin dimer (Craddock, 2009, 2010).

A second quantum MT model, advanced by Penrose and Hameroff, theorizes that quantum-superposed states develop in tubulin, remain coherent, and recruit progressively more superposed tubulin until a mass-time-energy threshold

(up to 500 msec) related to quantum gravity is reached. This model, linked to established interconnections between microtubules within each dendrite's cytoplasmic interior and microtubule-associated protein, predicts dendritic webs of approximately 100,000 neurons for discrete conscious moments occurring in synchronized frames every 25 msec (Hameroff, 1996). Dendritic webs are positioned to integrate and unify, on a brain-wide basis, fine scale processes comprising consciousness, insofar as many such fine scale processes (e.g. electromagnetic fields, calcium ion gradients, molecular reaction-diffusion patterns, actin sol-gel dynamics, glycolysis, classical microtubule information processing, and/or microtubule quantum computation with entanglement and quantum coherence) may extend through gap junctions and hence in principle throughout brain-wide dendritic webs. The concept of a "conscious pilot" refers to spatiotemporal envelopes of dendritic wave synchrony (demarcated by gap-junction-

defined “dendritic webs”) moving through the brain as the vehicle for a conscious agent which can experience and control otherwise non-conscious (autopilot) cognitive functions. The best measurable “neural correlate of consciousness” (NCC) is the EEG phenomenon known as gamma-synchrony, a term denoting coherent field potential

oscillations ranging from 30 to 90 Hertz (prototypically 40 Hz). Gamma synchrony along with consciousness apparently moves and evolves through various global distributions and brain regions, possibly mediated by “conscious pilot” wave propagation (Hameroff, 2010).

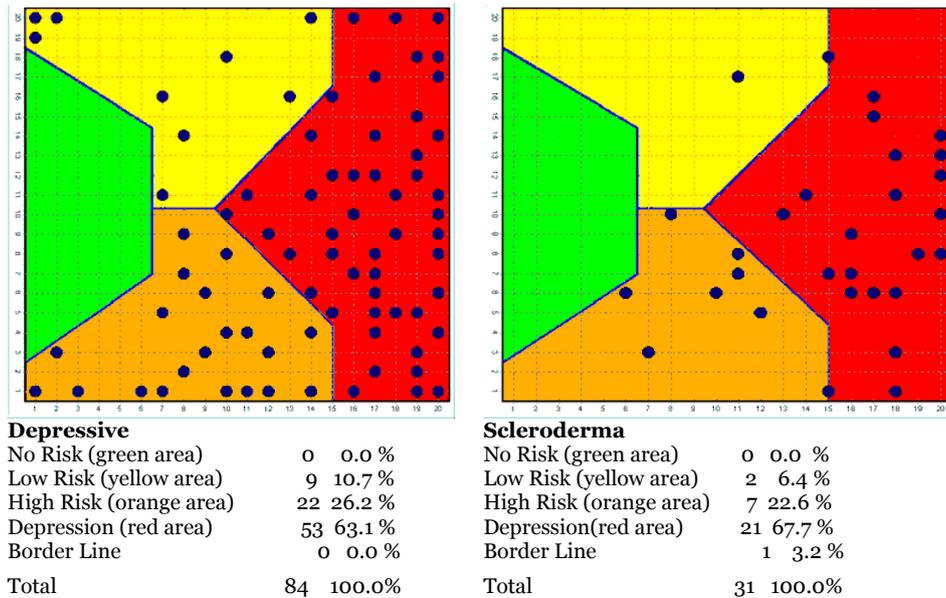


Figure 3. Description of the overlap of the fatty acid triplet (palmitic, linoleic and arachidonic) in scleroderma subjects compared to depressed subjects via the SOM of depression. It should be underscored that all the subjects of the original work carried a psychiatric diagnosis of major depression (MD), though it is also known that MD can be a misdiagnosis. We might expect that bipolar disorders could be classified within the orange area (work in progress).

According to Woolf *et al.*, (Woolf, 2010) MT dysfunction occurring in mental illness might be expected to cause abnormal tubulin oscillations between polymerization-depolymerization cycles resulting in different mixtures of arrays, classified by Craddock as types I–IV behaviors. Depression could result from insufficient type IV behavior and its associated information processing configurations. Given that billions of quantum computations in MTs may be commensurately responsible for moving millions of proteins over nanometer distances, with the most salient among the collective effects influencing neural activity on millisecond time scales, Woolf has concluded that “...classical and quantum information processing in brain MTs could be impaired in mental illness, to the extent that such information processing modes are validated by experimental support.”

Future research on EEG gamma synchrony as the neural correlate of consciousness (NCC) with reference to both healthy and depressed individuals along with the platelet fatty acid analysis elaborated through the Self Organizing Map (SOM) described below (Cocchi, 2008) might thus experimentally support a connection between our interactome hypothesis and operations of the cytoskeletal quantum-nanowire network.

5. Interactome Hypothesis Extensions

Does the interactome hypothesis of depression open up a new way to understand other pathological entities? In light of the biological considerations regarding depression herein developed, we might propose a heuristic hypothesis concerning other pathologies such as scleroderma that may be expressed as follows. Figure 3, using

the Self Organizing Map (SOM) for depression, displays a biochemical similarity apparently inhering between depression and scleroderma (Cocchi, 2008, 2010a,b). The figure demonstrates a strong similarity in the case distributions of depression and scleroderma; differences are related purely to differing abundances of sampled cases in the two alternative disease categories. The percentage of depressive disorder in scleroderma noted in the literature shows a striking correspondence with SOM data.

The SOM delineates molecular differences within the region of the same diagnosis, *i.e.* the red area which aggregates true MD according to uniform characteristics of platelet membrane viscosity (Cocchi, 2010; Tonello, 2010). A hypothesis that accurate diagnoses of MD include about the 60-70% of all the people currently labelled with MD (Bowden, 2001) could explain the SOM datum of 68.6% attached to MD found in scleroderma (Ostojic, 2007). The results obtained through platelet fatty acid markers for MD (red region) are very similar, yielding a 67.6% proportion of MD among scleroderma patients. However, all the scleroderma subjects fully correspond via the Self Organizing Map to the SOM classification for depression; this implies, in line with our hypothesis, that among cases of scleroderma the current standard psychiatric diagnostic scheme manifests difficulties parsing differences within the single diagnostic domain of MD.

Since the biochemical profile of platelet characteristics associated with the depressed population (Cocchi, 2010a, b) is the same as that linked with the population suffering from scleroderma, and since all people suffering from scleroderma appear to be depressed or to have mood disorders but not vice-versa (none of the MD subjects investigated had clinical dermatological signs of scleroderma), is it possible to conclude that proximate to a cultural origin of depression there also exists a parallel causally potent biological origin? Moreover, is it reasonable to postulate that depression may exert a causal impact on other dire somatic pathologies (e.g. Crohn's disease)? If not all of the depressed population has inflammatory bowel disease as appears to be the case for depression with respect to scleroderma, then it remains open to

question whether it is possible to connect the complex mechanism of depression to the onset of inflammatory bowel disease in a manner analogous to our reasoning regarding scleroderma, for which group there is a high depressed proportion of approximately 94% (Whitehead, 2002) taking into consideration also the involvement of serotonin (Zeller, 1982; Kimliuk, 1989). We may nevertheless compare membrane viscosity, serotonin receptor changes, and other molecular alterations of neurons within the brain to analogous biological domains of enteric neurons regarding conditions conducive to inflammatory bowel disease. The viscosity of the cell membrane might be a target for future research to better understand the complex phenomena that bi-directionally links brain and gut through serotonin and the dynamics of its transport within the brain-gut axis.

Conclusion

Fatty acids as platelet markers in psychiatry highlight a need to use higher mathematical tools such as artificial neural networks. One such tool in particular is the Kohonen Self Organizing Map (SOM); this instrument has yielded a dichotomous classification of subjects sorting as major depression versus euthymia and makes clear the complexity of the problem. The fatty acid triplet identified by SOM provides a means to map, through distinctions between states of saturated and of non-saturated platelet membrane, the membership of subjects into depressed versus euthymic categories. Other experimental findings show a biochemical typing in the dermatopathology of scleroderma comparable to that of depressed subjects. Our unpublished data suggests that a similar SOM overlap might be found in autoimmune diseases but not in ischemic cardiovascular disease.

These observations, in the light of work by Rasenick, Hameroff and others, suggest that viscosity of the membrane has a role in the molecular concomitants of depression and other disorders and in mediating the pharmacology of serotonin in neurons and platelets. However, such similarities between platelets and neurons are difficult to understand without an intervening

biochemical bridge, because serotonin cannot traverse the blood brain barrier. Therefore, it is necessary to postulate a common denominator underlying the low concentration of both neuronal and platelet serotonin in depression. Evidence for that kind of common denominator lies in the transfer of AA from platelets to brain and *vice versa*. Demonstration of bi-directional AA movement between platelets and neurons makes clear that specific conditions of modified membrane viscosity in these two cell types may affect the serotonin receptors in membranes. Experimental data show that euthymia correlates with higher viscosity while depression is associated with lower viscosity of lipid raft domains.

This observation, confirmed in the literature, allows construction of a stepwise molecular pattern in which the post-synaptic density interactome herein described may be rigorously connected to states of consciousness by the quantum cytoskeletal nanowire network and altered membrane fluidity, modifications of which are directly linked with the fatty acid profile of platelets. These molecular entities together engage the fundamental quantum substrates of consciousness through quantum computational variations potentially underlying, perhaps in measurable ways, different psychopathological conditions. Since the molecular circuitry described for neurons in the brain is similar to that of enteric neurons, and notwithstanding the fact that molecular pathways of enteric neurons lead to the regulation of alimentary functions while those of brain neurons lead to the mediation of consciousness, it seems

reasonable to infer that serotonin pathways leading from enterochromaffin cells to platelets through membrane viscosity modulated by fatty acids in ways similar to processes in brain neurons could represent a potent future research tool in explaining mood disorders and finding new psychopharmacological treatments. Furthermore, the measurement of gamma synchrony, coupled with quantitative analyses of the platelet fatty acid triplet and supplemented by the SOM instrument, may serve as a new test for determining quantum correlations with aberrations characteristic of psychiatric illness.

Consciousness and enteric functions are two phenomena at the foundations of both life itself and life's sensitivities to the prospect of death. Functionally identical molecular pathways within either of these two realms lead to superficially independent yet apparently interrelated processes that might plausibly communicate with each other in a profound way. We may be approaching a level of understanding that will enable us to identify a common helm of the two systems. If we can flesh out the details of this larger picture, we may then be able to open up a new entero-cerebral frontier of quantum approaches to the study of normal and pathological human consciousness.

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