The Strange History of a Nobel Prize Winner Who Predicted the Meaning of Research

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Abstract
This paper shares the history of a researcher and his groundbreaking discoveries which have been discussed for a long time that started during a conversation with a dear friend, Kary Mullis. Using biological markers, the research involved the ability to classify and differentiate depressive disorders from apparent normality. This research crossed the path of Kary Mullis, one of the most important scientists of the modern era, who discovered the PCR (Polymerase Chain Reaction), which initiated a fundamental step in the research of genetics. This paper also examines the contributions of other important scientists and how they were led to hypothesize that the molecular circuit of consciousness could open “the possibility of penetrating beyond the present classical-molecular theories about depression into the quantum domain of consciousness without throwing out what is already valuable in the standard paradigm,” as stated by Donald Mender in his groundbreaking paper titled “The Interactome Hypothesis of Depression.” Presently, the method utilized for the classification of depressive disorders has allowed, for the first time, the classification of the differentiation between bipolar disorder and major depression.

Key Words: artificial neural network, bipolar disorder, classic consciousness, Kary Mullis, major depression, quantum consciousness

Introduction
The strange story I am about to tell began in 2005. At the time, Kary Mullis was already well-known for his groundbreaking discovery on the Polymerase Chain Reaction (PCR) and I had been attending his lectures for nearly five years. But, who could predict what a conversation with a person of extraordinary intellectual power could mean for me – an obscure researcher in the biochemistry of nutrition. Frankly, this meeting turned into a friendship of such importance that I could not have predicted at that time, which all started with the mere pleasure of exchanging ideas, opinions, and concepts with an amazing scholar on one fateful day.

In that infamous year of 2005, I do not even know why I began, but I was inspired to analyze the platelet fatty acids of depressed subjects with my friend Lucio Tonello - a very bright mathematician. The

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ISSN 1303 5150
www.neuroquantology.com
biochemistry of fatty acids was my field of research, and much of the research conducted during my friend Scot’s time was showing good results, however, this previous research was far different from what I was about to do. For about three years I had talked with Kary Mullis about some of my ideas, who, in truth, did not even know what I was saying. However, one day in Milan in a bar near the university while drinking a Campari, we were honored to meet with a great friend of ours, Mario Tiengo, who asked me to explain the logic governing the biochemical metabolism of fatty acids in the body. We usually exchanged our ideas on paper towels, where he also had explained to me the whole basis of his new discovery that he was working on in the field of immunology. After this, I then told him what he wanted to know and understand about my work. This filled me with obvious pride that he, one of the world’s elite scientists, was asking me to explain my work with fatty acid metabolism.

Three years after that fateful day, our research took shape and many discussions took place with Kary Mullis that were very intense, and even sometimes dramatic. Friendship is one thing but science is something else, and sometimes things can get a little challenging if no-one is willing to compromise. In short, the below story overviews the focus of our research and discussions that took place which resulted in what was achieved. After reading this story, the title of the paper will become clear.

The research
In light of the recent article that seems to confirm the inevitability of the genetic origin of the depressive disorder (Karg, 2011), it is useful to retrace, briefly and chronologically, the steps that highlight the research on human and animal depression which was conducted by the research group at the institute of Paolo Sotgiu L.U.de.S. University, by the Faculty of Veterinary Medicine, and of the Department of Medical Veterinary Sciences of the University of Bologna. This research focused initially on the determination of platelet fatty acids isolating, as a characterization of depressive disorder compared with normal subjects, and was focused on three fatty acids (palmitic acid, linoleic acid, arachidonic acid) (Cocchi et al., 2008).

The results (Figure 1) obtained with the aid of an artificial neural network (SOM, Self Organizing Map, called ADAM), allowed for the later realization of a one-dimensional map which distributed all of the case studies in progress, using a coefficient that expresses the trend towards greater (normal subjects) or lower (depressed subjects) viscosity of the platelet’s membrane (Cocchi and Tonello, 2010a).

![Figure 1. Distribution of subjects (normal and depressed) on the SOM (two-dimensional), and SOM areas](image-url)

With these same procedures, (Self-Organizing Map, SOM called CAIN) because of the strong relationship between depression and heart disease, we examined if it was possible to distinguish between normal subjects (green) and ischemic (red) and if there were common points between...
depression and ischemic heart disease. These results confirmed the working hypothesis, as can be seen in Figures 2 and 3.

Figures 2 and 3. In the case of depression, the fatty acid triplet identified by the SOM (oleic acid, linoleic and arachidonic) divided (Figure 2) normal subjects (green) from non-ischemic (red) subjects, and found that after the release of all three groups of subjects investigated in a new SOM (green = normal, red = depressed, blue = ischemic), a common area was identified (depression and ischemic), characterized by reduced levels of oleic acid in platelets (Figure 3).

These findings were the first to indicate that ischemic pathology could be classified and that there was a quantitative element in common between depression and ischemia (Cocchi et al., 2007; Cocchi et al., 2008; Cocchi et al., 2009a; Cocchi and Tonello, 2010a; Cocchi et al., 2010b). The data on platelet fatty acids, found by the SOM as elements of the classification of depressive illness were obtained from the following formula:

\[ B_2 = \sum_{i=1}^{2} \left( \frac{A_i}{m_{w_i}} \right) \]

Where:
- \( A_i \) = per cent of i Fatty Acid
- \( m_{w_i} \) = molecular weight of i Fatty Acid
- \( m_{p_i} \) = melting point of i Fatty Acid

The index of each subject (called B2) distributed on a one-dimensional map gave the following result (Figure 4).
This step identifies the platelet membrane viscosity (Cocchi et al., 2010c; Heron, 1980; Lee, 1985) as a central evaluation feature, which leads to the formulation of the next hypothesis of the molecular pathway of depression. The molecular pathway of depression and how it impacts consciousness (Figure 5) was implemented as a result of discussions that took place between Kary Mullis, Mark Rasenick, and Stuart Hameroff. The results of these amazing conversations are revealed, showing clear experimental evidence between the element of conjunction with the amendments to the conscious state (Cocchi et al., 2010d).

Figure 5. Molecular hypothesis of consciousness.

Figure 5 shows the mathematical passages to explain the main cell molecular pathway that is involved in major depression (MD) and consciousness. According to the definition of linear and nonlinear mathematical models, the figure shows that from the membrane fatty acids to the tubulin, the phenomenon has a strong dependence on initial data (i.e., the viscosity of the membrane) (AA = arachidonic acid, LA = linoleic acid, PA = Palmitic acid). On this basis, it was our significant hypotheses that this is the molecular pathway of consciousness (Figure 6) and depression (Figures 7 and 8), utilizing the interpretation of quantum phenomena (Cocchi et al., 2010c; Tonello and Cocchi 2010).

Consciousness involves phenomenal experience, self-awareness, feelings, choices, control of actions, a model of the world, etc. But what is it? Is consciousness something specific or merely a byproduct of information processing? Whatever it is, consciousness is a multi-faceted puzzle. Despite enormous strides in behavioral and brain science, essential features of consciousness continue to elude explanations. (Hameroff, 1998, p. 119)

The following figure summarizes the mechanism of how quantum consciousness tries to reach the conscious mind.

Figure 6. Consciousness and unconsciousness. The unconscious, with global knowledge (the truth observable), is rich enough to give rise to creativity. The quantum information is drawn from the unconscious and then made available to the conscious mind as our classical information (From S. Hameroff, 1998: modified).

Figure 7. Schematic description of the way of serotonin from enterochromaffin cells to platelets and regulation of the interactoma. Through the viscosity of membrane under normal conditions.
The evidence for the hypotheses between experience and concept, allows for addressing the problem of serotonin and its consequences on the movement inside and outside the platelet and the neuron (it is known that serotonin does not pass through the blood brain barrier) as different manifestations of the phenomenon of conscious control, recognizing in the transport of arachidonic acid from platelet and neuron (Cocchi et al., 2009b; Cocchi et al., 2009c), the condition that, by changing the viscosity of the membrane, leads to a different input capacity of serotonin in respective cells (Cocchi et al., 2009d).

Two new issues are thoroughly reviewed, even on an experimental basis, and that is: animals and the role of depression in other diseases, as shown in Figure 9, from the devastating impact, both under subjective conditions as well as socio-economic aspects (Cocchi et al., 2009e; Cocchi et al., 2011).

It is shown, in fact, how scleroderma (Figure 10) is a phenomenon which originates from the depressive error (Cocchi et al., 2010a), with the possibility that this error is likely to be found in stem cells from which neurons and platelets originate (Cocchi et al., 2010e; Leonard, 2000). Indeed, both cells are of ectodermal origin.
The experimental considerations regarding the animal, going over the evaluation criteria used for humans, leads to the possibility of the existence of depressive phenomena in some species, and focuses on the guinea pig to explore the equally plausible hypothesis that the error is, in fact, in the stem cell (Cocchi et al. 2009d; Cocchi et al., 2010e; Schick and He, 1990; Schick and Schick 1981; Schick et al., 1990).

The membrane viscosity and the exchange of fatty acids between platelets and neurons, which determine the viscosity of the two districts, result in changing the binding capacity of serotonin, which appear as the conditioning elements of all the depressive disorders. This finding allows us to not only build a version of the molecular pathway of depression, but also provides concreteness to the hypothesis of serotonin as a factor of behavior regulation, both in animals and humans (Blardi et al., 2002; Herbert et al., 1983; Kaneda et al., 2001; Kovacic et al., 2008; Mann et al., 1992).

Based on this, in addition to the data in the literature, it is possible to construct a fascinating phylogenetic hypothesis.

The assumption is configured in the path leading to the crossing point, during phylogeny, where the circulating serotonin appears between cold-blooded and warm-blooded animals. Until man, in its relations with the possible molecular pathway of consciousness and its expression of different levels, to the classical and quantum aspects of the consciousness itself that can be measured using the gamma synchrony (Flynn et al., 2008).

In essence, the theory of Hameroff and Penrose suggests continuity to the properties of the molecular mechanism of consciousness, which is modulated by serotonin (Figure 11).

![Figure 10](image1.png)

**Figure 10.** Description of the possible link among stem cells, neurons, and platelets.

![Figure 11](image2.png)

**Figure 11.** Assumptions of the molecular pathway of consciousness in its relationship with serotonin, and possible evaluation, through the γ synchrony, of the different levels of consciousness (Cocchi et al., 2010e).

**Animal Consciousness: Between the Serotonergic System and the Quantum Aspects of the Cytoskeleton**

The existence of serotonergic neurons has been demonstrated in Drosophila (Lundell et al., 1996) in humans (Chugani and Muzik, 2000), and in vertebrates. Serotonin (5-HT), is involved in many bodily functions, such as, for example, sleep (Carley and Radulovacki, 1999; Portas et al., 2000), food intake, behavior (Wurtman and Wurtman, 1995), and the regulation of body temperature (AbdelFattah et al., 1997; Cronin and Baker, 1977; Myers, 1981). The decreased production of serotonin is strictly associated with depressed behavior, while the increased formation of kynurenines may contribute to the development of a late onset of depression through their apoptotic, oxidative, and neurotoxic effects, and through the up regulation of the nitric oxide synthase, phospholipase A2, Arachidonic Acid, prostaglandins, 5- lipoxygenase and leukotrienes production (Oxenkrug, 2010).

The interesting work of Spurej Maurer (2005) draws a strong correlation between circulating serotonin and animal evolution.
In light of experimental evidence, Maurer-Spurej suggests that the presence of serotonin, as a circulating factor of the temperature, indicates the evolutionary turning point between reptile species and warm-blooded animals, a phenomenon which, in fact, could coincide with the emergence of an endothermic condition (Figure 12).

The phylogenetic comparison between animals with and without circulating serotonin, makes it plausible, even for animals, that the hypothesis of molecular and quantum consciousness may be applicable to both humans and animals, though, at different levels of expression.

Assuming that consciousness is realized through the quantum mechanisms of cytoskeleton, we could say that potential consciousness could be expressed by each cell which is equipped with the cytoskeleton in any animal species, and that this could be the biological interface, supporting the vision of consciousness as interpreted by Manousakis (2006). Therefore, different expressions of the potential levels of consciousness might occur, according to the evidence referenced above.

These considerations should, however, be substantiated as follows: The Orch OR Theory requires the presence of at least 300 neurons, as a minimum level to express conscious states, which corresponds to 100 milliseconds of "quantum coherence," and then it is unlikely that we can speak of "true consciousness" in paramecium. In addition, the paramecium does have a mature, but primitive form of cytoskeleton (tubulin-based circuits) (Hameroff, 1998). A kind of "pre conscious protein" based on quantum computation could be a condition of evolutionary continuity among living organisms.

The scientific debate on the Orch OR Theory has never considered the role of serotonin in living species, and whether they have or not, circulating serotonin. The human and animal consciousness, therefore, should be considered and discussed with respect to the pre- and post-circulating serotonin (Figure 14).
Cocchi M., The strange history of a Nobel prize winner

Figure 13. Schematic representation of possible interactions-modifications among neurons, platelets, fatty acids, and cellular interactome in depressive disorders, in addition to consciousness changes.

In animal models, in agreement with the anatomy and physiology of organisms and the presence of circulating serotonin, one might think that only at the transition between cold-blooded and warm-blooded (Maurer-Spurej, 2005), animal consciousness could begin to take on characteristics of growing complexity. From Drosophila to Man, it has been well documented that the presence of serotonergic neurons phylogenetically very early (Azmitia, 2001; Jacobs and Azmitia, 1992). The first evidence of the presence of serotonin has been found in thrombocytes of birds and three species of reptiles, the endothermic leatherback sea turtle, the green sea turtle, and the american alligator, which are partially endothermic (Maurer-Spurej, 2005).

The available evidence suggests that, in vertebrates, serotonin-containing enterochromaffin cells are lacking only where there are innervations of the intestinal mucosa by nerve fibers that contain high concentrations of serotonin (Anderson and Campbell, 1988). At this point, a thought arises: Is the late onset of circulating serotonin the watershed between classic consciousness and quantum consciousness?

This will confirm the hypothesis of the existence of a watershed in the evolution of consciousness, giving continuity to the properties of the molecular mechanisms of consciousness with the Orch OR Theory, from primitive conditions to those more advanced. A submerged animal consciousness which sees, probably, in tubulin and microtubule a self-determination of the state of consciousness, restricted to what is necessary to exist.
without emotional expressions and, this, faces an increase of consciousness (neurocorrelate, classic information) leading to emotional expressions of consciousness, more complex and differentiated, with respect to a condition of an increasing critical mass ratio among tubulin, synapses, cortex, and serotonin.

This would generate the molecular circumstances that give dimensions to the phenomenon of "consciousness" for those aspects that interface with the man and his environment with his perceptions in a complex scalability that, from man goes back to the animals that have marked the endothermic turning point and to the animal categories that took place earlier, where the dimension of consciousness becomes more and more elementary, limiting it to the strict needs of those animals that represent the pre and circulating serotonin age, up to man.

The exact mechanism by which serotonin may influence the consciousness or behavior is not yet clear for today's science, although there is evidence of a relationship between serotonin and tubulin in psychiatric disorders (Azmitia, 2001; Crespi, 2010) as well as between cytoskeletons and the brain (Bond and Woods, 2006; Cronly-Dillon and Perry, 1979).

Accepting the evidence referenced above, together with the fact that consciousness may be expressed through the conditions of the state of tubulin (as reflected by its proximity to the molecular structure of the cell), we must assume that each neuron of any animal species, with its cytoskeleton, is endowed with the same power of consciousness. It is, therefore, clear that different levels of potential expression of consciousness might occur. Virtually, even in the most basic forms of life there may exist a potential of consciousness that expresses itself and is limited to the needs of the living.

All this would be a condition of continuity between living organisms, without affecting the meaning of creation, reported from Genesis (1, 25), of the animals' categories but confirming the concept:

\[
\text{Et fecit Deus bestias terrae iuxta species suas et iumenta secundum species suas et omne reptile terrae in genere suo...},
\]

and of man: ... formavit Dominus Deus hominem pulverem de humo et inspiravit in nares eius spiraculum vitae, et factus est homo in animam viventem... (Genesis, 2:7).

Only man would have had that breath of life that, in terms of biological interpretation, could mean the optimization of a critical mass ratio among tubulin, synapses, cortex, and serotonin.

As part of the above considerations, we believe that, in the dynamics of the process of consciousness, that serotonin should also be considered due to its aspects of modulation of the intensity of mood disorders as well as the different types of psychotic disorders. For methodological clarification, it is necessary to recall here our view on consciousness, which is understood as a complex system, organicistic and interactionist, in which the parties can be explained only if they refer to the whole.

In detail, ordinary consciousness can be represented as a set of levels that are consequential and communicating:

1. Pure biological level or primordial ego: the proto self of Damasio (1999), attributing in a rudimentary form to his own ego, feelings of hunger, thirst, pleasure, pain;
2. Bio-eco-logical level: the conscious interaction between subject and environment, but set only the "hic et nunc" with no extension project.
3. Extended mnemonic level: belonging to a consciousness that, while expanding "back and forth," does not yet embody in a language its being continuous narrative, preserved by the memory as a place of meaning of life.
4. Level of identity sense: from its original roots in biology the ego has gradually expanded to the ecological dimension or mnemonic short-range, is then passed to the mnemonic long-haul dimension, and now, through language, produces an accomplished culture.

In other words, the ego produces articulations of sense about oneself and the world that is incorporated into his/her experiences and his/her
acting out, in a narrative, intellectual and emotional, irreducible to any other, world views, social stress, scientific and cultural expressions.

5. Mystic level of consciousness or abyss of consciousness (Cocchi et al., 2009d). The presence in humans of a prophetic intuition, of an abyss of consciousness opens the way for intellectual freedom as liberation from the outer limits (subject, "obstacles" to overcome in pursuit of their projects) and internal (indeinitely biological determinism or panbiologism).

Man is rooted in biology, but this does not solve it in its entire existence. In short, it is reductionist to identify the personal self in a simple chain of neurons or, in other words, to explain the mind, and thus indirectly the soul/consciousness, only on a neural basis (e.g., on neuro-psychoanalysis and on Freud’s old dream of reducing the mental to the neural) (see the contributions of Henrich et al., 2010 and Semenza, 2010).

On the other hand, obviously, ontologically nonsensical undock the ego from his flesh, from its biological dimension. There is, in short, a carnal “self,” but also a “self” whose nature is immaterial, a-quantum, mysterious, chaste guardian of freedom and openness to a transcendent sense:

On the idea of soul we must say the following. To explain what it is, would be task of a divine exposure in all directions, and long; but, to say what it looks like is a human exposure, and relatively short. (Plato, Phaedrus, 246 A it. tr. G. Reale; see also Heraclitus, fr. 45; compare also the intuition of Heraclitus' logos, which increases itself: fr. 115 and the pace of the Platonic Phaedo, 99 A-B).

In this context, as can be inferred from the subsequent molecular biology argument, the dialectic among tubulin, brain and synapses, governed by serotonin, could be the privileged hermeneutical key to determining the different levels of states of consciousness (Figura 15). In our case, animal consciousness could be incorporated at the pure organic and bio-eco-logical levels (Bekoff and Allen, 1997; Bekoff et al., 2002; Bekoff and Pierce 2009; Dennett, 1996; Gozzano, 2001; Griffin, 1992; Wilder, 1996).

It is even believed that animals show a wide range of moral behavior, including sense of justice, empathy, trust, and reciprocity: A hypothesis that would lead us to an even higher level of consciousness, to the extent that morality would be understood as an evolutionary trait that humans share with other social mammals. Quaranta et al. (2007) argue, on the other hand, that the lateralization that appeared before language is not just a prerogative of man, but also of very different organisms (i.e., dogs).

Mascalzoni et al. (2010), who studied chicks (the chicken), concluded that the brains of vertebrates have an innate neural mechanism underlying the recognition of animate objects (along with physical causality, and that the distinction between animate and inanimate objects constitutes a kind of Kantian genetic a priori). In accordance with these studies, this expands the concept of “animal potential memory” and one could hypothesize a sort of proto level of animal consciousness (extended mnemonic proto level).

Even in the world of plants, one could speak of a first level of consciousness. Tryptophan, in fact, together with some plant intermediates (oxygen and reduced cofactors), form serotonin. The role of all these is to ensure the utilization of light, which is essential for life (Azmitia, 2001). In fact, as a proto-self exists in animals and humans which is linked to the fulfillment of basic living needs (hunger, thirst, pleasure, pain), so there is a sort of pre - proto-self
plant, which is an expression of the dialectic-tryptophan-intermediate substances-serotonin-light, which guarantees a biological life. Serotonin, with all of its dynamics, would, therefore, constitute the principle of identity of the plant: The plant lives because the serotonin guarantees the light. In other words, you could also split the pure biological level into the following:

- primordial consciousness plant or pre-proto-self.
- primordial animal and human consciousness or proto-self.

The Spinoza conatus sese conservandi, the power that every natural expression has to expand its power, in primis the existence, is therefore, transversal to all of nature and seems to impose itself as an original marker of consciousness in its original announcement, that is, to say “from” and “in the very moment” we start talking about it.

In conclusion, it appears that the existence of a genetic error (several times hypothesized, and, nowadays assumed with reasonable certainty), may result in an incredible logical sequence of events, like a waterfall, which allows us to define the context of the depressive disorder in the human and animal world, in its molecular, quantum, philosophical, and religious aspects.

Conclusion
After much long thinking, the development of a complex, plausible mechanism that could explain the delicate molecular steps, encouraged by the valuable support and contributions from friends (Fabio Gabrielli, Massimo Pregnolato and Eliano Pessa), seemed to define the possible picture of the complexity of psychopathology. All of this was stimulated by the magic and prophetic words of Kary Mullis.

It is a very important discovery. Just think that, through this method it will be possible to understand if a patient will have intention to commit suicide. It is a philosophic, medical and religious revolution (K.B. Mullis, Interview by Marco Pivato, Ma la depressione è nel sangue, La Stampa, Tuttoscienze, 2008, October 1, V).

Kary Mullis goes on to further state:
As this work progresses, it will not be at all surprising if new strategies arise for treatments. We may be at one of those turning points which is always subtle at first, but turns into a torrent very quickly. Keep your eyes on those little balls of fat. Something is about to happen. (Il Resto del Carlino, May 28, 2008, La Stampa, Tuttoscienze, 2008, October 1, V).

Those words, "something is about to happen" took shape three years later, as it is now 2011, and the occurrence of the achievement of the classification, for the first time in the world, of the differentiation between bipolar and depressed subjects using a magic strategy between biology and mathematics, is now in place. While enjoying a good glass of wine with Kary in my home, Kary advised me that I should do nothing further, but instead let other researchers proceed with this work, like he did after his discovery. I still question to this day whether an unknown biochemist (myself) and mathematicien (Lucio), would be where we are at today with this research if that infamous meeting at the bar with Kary Mullis in 2008 would not have occurred. Was it a coincidence? No one knows how much the association with Kary Mullis could have affected my work, which resulted in achieving significant results. Could this, perhaps, go on to receive a Nobel Piece prize? As of now I cannot predict, so I will leave that for the reader to ponder.
Karg K, Burmeister M, Shedden K, Sen S. The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited. Arch Gen Psychiatry 2011; Published online January 3.