

# Empedocles: neurophilosophy and neurosciences-prophecy and reality

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## Editorial

Neurosciences are extended into a broad field, where the scientific observation and research join harmoniously the imagination, the intuition, the philosophy, the critic analysis, the enthusiasm and the skepticism, opening new horizons in the theoretic perspectives and offering new motivations for research, on the bases of an advanced multi-dimensional intellectuality. From the Era of Pre-Socratic philosophers, soul and mind have been the subject of continuous speculation, study, research and meditation.<sup>1</sup> Questions that the human being posed to himself, concerning the existence, the soul, the psychosomatic entity, the cognition, the knowledge of the world, and the perception of time and space used to exercise always an existential anxiety.

Very frequently, human emotions have been the foci of insisting endeavors for right interpretation and detailed analysis. Reasonably, the importance of the mental activities and interior feelings on the psychosomatic homeostasis are subjects of inquiry from the Greek antiquity up to our Era.<sup>2</sup> Among the pre-Socratic philosophers Empedocles may be considered as the most proximate to Neurosciences. He was younger than Heraclitus<sup>3</sup> and older than Socrates, born in the city of Acragas (Agrigento, Sicily) one of the most prosperous and beautiful cities of the "Grecia Magna", in 492 BC. We don't know any detail of Empedocles' life. Diogenes Laertius' records on Empedocles are intermixed with myths, stories and legends of contradictory character.<sup>4,5</sup> From all the records, we can conclude that Empedocles was philosopher, physician and priest, mystic and prophet, poet of a high talent, brilliant orator, man of exceptional knowledge, characterized by generosity and magnanimity, who attempted to associate philosophy with science.

Empedocles writings are mainly summarized in two poems, written in hexameter verse.<sup>6</sup> One of them was entitled "On Nature" and the other "Purifications".<sup>7,8</sup> The poem on Nature has an obvious cosmologic character, introducing at the same time the main principles of evolutionary ontology. The other poems entitle "Purifications" has a strong religious character. From the two poems only 450 lines, in fragments, have been survived, which are strong enough for revealing the philosophical principles, the clarity of the mind, the enthusiastic character of the philosopher and the influences by Heraclitus<sup>9</sup> and Parmenides.<sup>10,11</sup> Some of Empedocles' concepts may also be attributed to Anaximander and Pythagoras, while his methodology may be attributed to Anaxagoras.

Empedocles endeavored to enter in the depths of the human soul in order to discover the interior power which motivates the emotions, the feelings and the social behavior of the human being. He tried to identify the main pivots of the emotional interactions. He insisted that Love and Strife are the ends of an axis, which regulates and controls all the spectrum of the human emotions. According to Empedocles

there is not birth or coming into existence and death. There is only a connection or mixture and separation of four pure fundamental elements or "roots", which are "the earth", "the air", "the fire" and "the water". According to Aristotle these four elements, which have been traditional concepts in Greek physical theory,<sup>12</sup> were mentioned first by Empedocles. The theory of the four fundamental elements or roots is not far from the scientific reality, since earth symbolizes the carbon (C), the basis of any organic substance, the water (H<sub>2</sub>O) and the air (O<sub>2</sub>) are also essential elements of the life and the fire created from the union of carbon with oxygen is the source of energy for any activity in life (circle of Krebs).

These four essential ingredients are simple, unalterable, eternal and well balanced. The main forces of universal value which provoke the mixture and the separations of the four fundamental elements are Love and Strife. These are the eternal powers which control mixing and unmixing of all elements.

Love is the connecting power. The elements are united, blended and harmoniously intermixed under the beneficial agency of Love. Which pervades the universe and acts as the moving power of the human life. There is no transition from the existence in to nothingness, but only a ceaseless interchange of successive existences, controlled by the alternating domination of Love and Strife. All the creation is based on the Love and any tendency for development of a harmonious,<sup>13</sup> rational society, characterized by friendship, kindness and perfect collaboration is also based on Love.

Strife induces the enmity, the hostility, the separation and the chaos. It causes alteration, transformation and separation of the global unity into separated masses which are destined to disintegration. Strife can separate even the members of the body and the elements of the soul. The two "powers" exist and would exist for ever in a continuous opposition, exchanging and replacing each other in a round way, exercising a strong influence on the balance of the universe and the homeostasis of the human soul. These two forces control the

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continuous interchange of life and death. Everything suffers from the contradiction and rivalry between Love and Strife, which control the cosmic cycle of continuous alterations. As long as the conflict between Love and Strife would last, the human being shall remain prisoner and captive of his own passions, unable to find the real way of his life, unable to establish in self the interior peace and harmony. He would have the feelings of pleasure and pain alternatively. The suffering of the universe and the anxiety and agony of the human soul never cease, due to perpetual exchange of preponderance between Love and Strife, unless the connecting power of Love succeeds to dominate eventually establishing the peace, the friendship, the unity and the concreteness and everything would come into "one" under love.

Without Love the man is enclosed in an unfamiliar tunic of flesh and an exile from the territory of harmony and serenity.<sup>14</sup> He is far from the wealth of divine understanding, a servant of passions, fear, instability, threat,<sup>15</sup> succumbed to homicide.<sup>16</sup>

The happiness and the exhilaration are attributed to Love, which is the omnipotent force acting in balance and harmony, which penetrates deeply the members of the human body and the soul as a genuine purifying power. The unity and solidity of the human existence is virtually based on the unifying power of Love (Frag. 19).

Empedocles claimed that ontogenesis under the power of Love results in creation of perfect entities, bodies and faces, whereas under the influence of Strife it results in malformations and congenital defects in humans, animals and plants. As biologist, Empedocles described the chimeric creatures, such as man-faced bulls, the teratogenesis in many creatures with a face and breasts on both sides, the hermaphroditism with male and female nature combined the malformations of the limbs of the body and the hybrid forms.

Thus he proceeded to detailed descriptions of morphological alterations, of separation of members of the body, stating that "many neckless heads are extended up, bare arms wandered detached from the shoulders, and eyes wandered alone, outside of faces" (Frag. B57), which remind Aristotle,<sup>17</sup> works of modern biologists and anthropologists, the consequences of the recent interventions in the human genome and Picasso's "Guernica". The tissues of the body, the viscera and the limbs are composed by essential elements which are intermixed and interrelated in equivalence.

Empedocles attempted to understand the physiology of respiration and the blood circulation, the function of the heart and the blood supply of the brain. He described also the material nature of air and the relationship between air and water in the bright metaphor of the double-bell (clepsydra) (Frag. 91 (100)).<sup>18</sup>

Empedocles described the Globe (Sphere or Sphaera) as a god-like entity, as a prototype stereoscopic image of the unity and harmony, of the completeness and self-sufficiency, according to Orphic concept of friendly collaboration of all ingredients,<sup>19</sup> which are connected together with the strong links of Love, composing the "One".<sup>20</sup> The Globe is a symbol of unanimity, equality, equivalence and harmonious homeostatic state. On the other hand Globus may symbolize the generation of the soul<sup>14</sup> and the eschatological restoration of everything within the bounds of harmony, tranquility and reason. Empedocles claimed that there was a stage in which Love was dominant and all things were unified and intermingled with one another into a Sphere in a cosmic harmony. Unfortunately Strife separated the elements in a later time inducing mortality and decay. That, in fact, was the beginning of cosmogony.<sup>21,22</sup>

Empedocles underlined that the continuous controversy troubles and trials the human soul and disturbs thoughts and emotions

(Frag.114). It is true, that problematizing and disputing are essential in scientific research especially in the field of Neurosciences. Many years later, the skeptics, such as Sextus Empiricus<sup>23</sup> claimed that controversy is the theoretical basis of Science and Philosophy and they tried to deliberate the thinker from the dogmatism and the anxiety and depression, which are derived from the fixation on inflexible doctrines and axioms, encouraging him to proceed to a continuous search for the truth.<sup>24</sup>

In the field of the biological sciences Empedocles' theory of the four "roots" which have equal validity and importance, as the basic elements of the creation and the life is of existential importance.

The earth, the fire, the air and the water are the essential elements of living creatures. They symbolize at the same time the unity and the multiplicity. The lack or the separation of one of them is incompatible with the continuation of the life.

In terms of cell organization, the harmonious coexistence of all Empedocles' "roots" occurs in the mitochondria of the cell, which are the most essential organelles for the living entities, since they are the source of energy production and the main factor of cellular homeostasis, cellular differentiation and continuation of the viability of the cell.

The Empedocles' four roots are connected tightly in the membrane systems of mitochondria. The "earth" symbolizes the proteins, the lipids, the calcium, the iron and the other metals and ions of the outer and inner mitochondrial membranes and matrix. The main role of mitochondrion is the production of ATP from glucose. The energy production by glucose metabolism, as well as the electron transport chain represent Empedocles' "fire", which never ceases, as long as the cell is alive. The "proton leak" in the mitochondrion, which is mediated by a proton channel called "thermogenin" contributes also in heat production as a focus of fire,<sup>25</sup> The "air" which symbolize the oxygen (O<sub>2</sub>) is essential for oxidative phosphorylation and redox reactions through electron transport chains in the inter-membrane system of mitochondria.<sup>26</sup> The "water"<sup>27</sup> is continuously produced in the mitochondrion by cytochrome c oxidase, (complex IV),<sup>28</sup> which is the final protein complex in the respiratory chain and transfers electrons to oxygen, establishing therefore an electrochemical equilibrium in the cell.<sup>29,30</sup>

The role of Calcium homeostasis (Frag.6) by mitochondrial activity is essential for the viability of the cell and the cell signaling, which is of fundamental importance for the neurons, which continuously exchange informations, in the context of numerous short or long neuronal circuits, using large number of neurotransmitters, receptors and ion channels.<sup>31</sup> Mitochondrial activity protects the cell from excitotoxicity, degeneration and eventual apoptosis,<sup>32</sup> which would have tragic consequences for the function of the brain. On the other hand calcium in mitochondria, "the earth", contributes in energy production,<sup>33</sup> activating the enzymes of the oxidative phosphorylation to reform ATP.

Mitochondria, therefore, are essential for the continuity of the life and the integrity of the cell. The gradual degeneration of mitochondria is associated with aging and a substantial number of neurological debilitating disorders,<sup>34</sup> such as Alzheimer's disease,<sup>35</sup> Parkinson's disease, Huntington's chorea<sup>36</sup> and many others, which cause tragic deterioration of the quality of life.

Empedocles' philosophy inserts in the depths of brain function, concerning emotion and behavior. It enters in the limbic system,<sup>37</sup> which is consisted of evolutionarily archaic brain structures, closely associated with personality, morality, motivations, memory, emotions and human social behavior.<sup>38</sup>

The two poles of the human emotional activity and moral consciousness, which play the most important role in the interior life and social behavior, are the feelings of Love and Strife, which have been extensively described and emphasized by Empedocles. Both of those feelings are related to neuronal circuits of limbic system and the other emotion-memory related neuronal structures of the brain.<sup>37</sup> Neuronal circuits of amygdala are particularly involved<sup>39</sup> in emerging emotion and behavior with the coordinated activity of many cortical and subcortical structures of the brain,<sup>40</sup> including the prefrontal area of the frontal cortex,<sup>41</sup> areas of the temporal isocortex<sup>42</sup> and the hippocampus.<sup>43</sup>

Among the neuronal networks of amygdala, the basic lateral nucleus (BLA) seems to play an important role in the differentiation of the primitive emotional impulses, on the basis of the senso-sensorial experiences of the individual,<sup>44</sup> whereas the central nucleus is mostly involved in emotional reliability and responses of the autonomic nervous system to emotional impulses. Therefore Love and Strife are reinforced by exterior stimuli, related to environmental conditions. The orbitofrontal cortex is also important in the modulation of behavior, under emotional impulses, associated with external visuo-auditory and olfactory stimuli. The posterior cingulate cortex plays a crucial role in supporting internally-directed cognition and in modulating social behavior, in collaboration with anterior cingulate cortex, which is involved in emotional regulations and self-transcendence,<sup>45</sup> exteriorizing either Love or Strife.

Amygdala, as an anatomical structure, is global like the Empedocles' "Spheros" or the "Globe" of Parmenides, which symbolize the unity and the solitude of "Being". Under the feeling of Love the human being is solid and compact, since the connective power of the love, associated with happiness makes tight links among the elements of the entity, resulting in a harmonious unity of the soul, like a perfect "Globe" of Being.

Later, whenever negative emotions, like Strife, penetrate the soul, an alteration of the simplicity and unity of the soul occurs, resulting in an obvious fragmentation of the Being. The negative emotions are emerged from the structures of the limbic system. The augmentation of the Strife results in the augmentation of the interior contradictions and the fragmentation of the global solidity of the soul.

A vortex occupies the soul whenever the Strife dominates in the world and in the human mind.<sup>46</sup> Then the interior harmony and the homeostatic equilibrium are lost. The motionless tranquility and serenity of the Being is lost. It is replaced, as a rule, by fear, which is emerged from the amygdala<sup>47</sup> under the influence of unpleasant impressions and messages,<sup>48</sup> which change the interior order and induce the anxiety, the instability, the fear, the treat and the existential insecurity.

The dramatic phenomena of the conflict of emotions in the human soul, the interior contradictions, the multiple and multiform alterations, the fluctuations of the mood and behavior are the tragic consequences of the rivalry and perpetual antagonism between Love and Strife. The Love unifies, composes, harmonizes, combats the fear and the tread, constructs, globalizes, establishes the truth in the consciousness of the human being induces the liberty, the friendship and the fraternity in the human society, directs the man's efforts to peace, kindness, solidarity and compassion, whereas the Strife induces the interior fragmentation, the deceit, the envy, the unsteadiness and the ceaseless fluctuations, the changeability of mind, the anxiety, the hostility, the anger, the social aggression and the interior decay, eventually.

Empedocles is a prototype of moral philosopher as well as a neuro-

philosopher.<sup>49</sup> He attempted to interpret the reason of the continuous alteration of the human emotions and the perpetual conflict between Love and Strife, in the depths of the human existence. He claimed that the dispute and rivalry between Love and Strife is the main cause of interchange of happiness and pain, peace and aggression, kindness and envy, friendship and enmity, serenity and anxiety, unity and fragmentation, hope and despair, integrity and decay in the human life.<sup>50</sup>

Empedocles discovering the Strife in himself, been deprived from the interior harmony and homeostatic equilibrium, admitted that he was a human being, mortal, wondering in the world like an exile and fugitive, "interchanging his paths", "an exile from the gods and wanderer" (Frag.115.13) in a condition of depersonalization, a simple miserable member of the creation inside the natural world, like a fish outside the sea (Frag.118). He considered himself as a dishonest detainee captive in a cave, as a slave to his passions and interior conflicts. However, feeling and understanding the Love he acknowledged that the spiritual culture and the wisdom elevate the human being and restore his ancient spiritual beauty. The interior harmony, the high mentality, the peace and serenity of the soul shine and pacify the human society. Therefore, blessed is he who possess the treasure of wisdom and his thoughts are inspired by divinity.<sup>51,52</sup>

Never the less, Empedocles recognized in a state of self-evaluation, that in spite of the continuous efforts for spiritual culture and wisdom, it is very hard, even impossible, for the man to approach the divinity (Frag.133). Although deification might be the center of the ideals and expectations of the human being, this is unfeasible practically, since God is Spirit, impossible to be described by man, beyond any anthropomorphic and anthropometric concept and description. It is enough for the human being to avoid malevolence (Frag.144) and to adapt his human nature peacefully, endeavoring to culture the virtues and values perpetually.<sup>53</sup>

Empedocles theories exercised an important influence in the European philosophy. Thinkers like Kant and Nietzsche.<sup>54-57</sup> were inspired by Empedocles' philosophical doctrines widely. In Nietzsche's philosophy good and evil, strength and weakness, freedom and subordination, Apollonian and Dionysian spirit interchange and dispute like the Empedoclean Love and Strife, modulating human behavior.

Although Alcmaion from Croton is considered as the first neuroscientist and neuro-philosopher,<sup>58,59</sup> in reality Empedocles is the philosopher, who entered in the depths of the human soul, attempting to interpret the motives of the patterns of the human behavior. Empedocles is the first neuroscientist who, in a symbolic and vivid schematic way, described the "sphere", the global and circular shape of the limbic system, as the center of the feelings and the human behavior,<sup>60-62</sup> and as a place of contradictions and interior conflicts between love and hate, peace and fight, calmness and fear, tranquility and uneasiness, good and evil, symmetry and asymmetry.<sup>63</sup> During his life Empedocles searched for the pure and genuine knowledge and tried to find the answers of main questions and problems, which concern cosmogony, cosmology, ontology, anthropology, morality and ethics, human behavior and sociology.<sup>64</sup>

Empedocles work is characterized by accurate observation, acute and concrete thinking, rich poetical word and ability to penetrate deeply the human soul and to touch the most sensitive and mystic interior cords.

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## Conflicts of interest

None.

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