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"Too Soon on Earth": A Biophilosophical Model of Schizophrenia. Some Implications for Humanoid Robots

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Abstract

This paper presents a new explanatory model for schizophrenia based upon philosophical, molecular and neurobiological hypotheses as well as on years of experience in observing and treating these patients. To start with, a novel interpretation of the Hegelian concept of mediation is presented. Mediation is defined as the rejection of non-realizable programs, such as thoughts and ideas, at a certain point in time in the evolution of a living system. Whenever a system treats non-realizable programs as if they were realizable, its ability to "test the reality" is lost, and consequently a loss of ego-boundaries may occur. On the molecular level, I will try to show how "non-splicing" of introns during the mRNA splicing process is equivalent to a loss of the rejection function corresponding to mediation. At the cellular level in the brain, mediation can be explained in terms of glial-neuronal interactions. Glia exert a spatio-temporal boundary setting function determining the grouping of neurons into functional units. Mutations in genes that result in non-splicing of introns can produce truncated ("chimeric") neurotransmitter receptors. I propose that such dysfunctional receptors are generated in glial cells and that they cannot interact properly with their cognate neurotransmitters. The glia will then lose their inhibitory-rejecting function with respect to the information processing within neuronal networks. This loss of glial boundary setting could be an explanation for the loss of ego or body boundaries in schizophrenia. Pertinent examples of case studies are given attempting to deduce the main symptoms of schizophrenia from the proposed hypothesis. Some implications for the design of delusional robots are also discussed. Finally, the evolutionary potency of non-coding introns is philosophically interpreted that schizophrenics may be "too soon on earth".

Keywords

Non-Splicing of Introns, Chimeric Glial Receptors, Loss of Glial Boundary

Setting, Disordered Mediation, Loss of Ego-Boundaries, Schizophrenia, Evolutionary Potency, Delusional Robots

1. Introduction

The primary symptoms of acute schizophrenia for which an explanation must still be sought include the occurrence of hallucinations, delusions and thought disorder [1]. There are numerous hypotheses concerning the etiology of schizophrenia, most of which focus on biological, psychological and sociological factors [2]. However, the presumption that schizophrenia has a multifactorial etiology arising from a combination of various factors tends to force itself upon most clinically versatile psychiatrists [3]. Explanatory models of this psychobiological disorder should, therefore, be based upon an interdisciplinary approach. My explanatory approach to the schizophrenic disorder and symptomatology is based upon philosophical, molecular and neurobiological hypotheses as well as on years of experience in observing and treating these patients.

I will start out with the philosophical concept of "mediation" as stated by Hegel [4] [5]. According to my novel interpretation, mediation means the rejection of non-feasible (non-realizable) programs (thoughts, ideas) at a certain point in time in the evolution of a living system. Here the cybernetic principle of feasibility [6] [7] plays a central role. Whenever a system treats non-realizable programs as if they were realizable, then its ability to "test the reality" is lost. This disturbance is caused by the fact that the system fails to reject non-realizable programs.

I hypothesize that schizophrenia is a disorder caused by dysfunction of the mediation mechanism. Supposing that schizophrenic symptoms are due to serious brain dysfunction with a biological basis [8] [9] [10], it should be possible to demonstrate how mediation functions on a molecular and cellular level and how dysfunction of the mediation mechanism occurs.

On the molecular level, it will be shown in the context of mRNA splicing that a "non-splicing" of introns is equivalent to a loss of the rejection function corresponding to mediation [11]. This in turn leads to the production of an aberrant protein, which in some cases could result in a truncated receptor being expressed on the surface of a neuron or glial cell [12] [13]. In addition, inclusion of introns (retention) in our genes generates increased protein diversity [14].

On the cellular level, the mediation process in the brain can be explained as a glial-neuronal interaction. This means that a spatio-temporal boundary-setting function is attributed to the glial cells (astrocytes, oligodendrocytes), such that the glial cells determine the grouping of neurons into functional units [15] [16]. If we suppose that "chimeric" (truncated) receptors are generated and expressed on the surface of glial cells, these receptors cannot be occupied by their cognate ligands resulting in glia that lose their inhibitory-rejecting function with respect to the information processing within neuronal networks. This boundary loss af-

fects many brain areas simultaneously in schizophrenia (for review see [17]), such that the brain structuring in functional domains is almost completely lost, explanatory for the model for the "loss of ego or body boundaries" in schizophrenia.

Next, I will attempt to elaborate on these hypotheses in detail in order to deduce the essential symptomatology of schizophrenia from case studies. Furthermore, some implications for the design of "delusional" robots will also be considered. In conclusion, the high evolutionary potency of introns may allow the philosophical interpretation that schizophrenics are "too soon on earth".

2. Mediation as Rejection of Non-Realizable Programs

The concept of mediation plays a central role in philosophy. Mediation means the designation of a mediator for the purpose of combining opposite perceptions or contradictory conceptions [18]. Here we are dealing with a general cognitive statement practically devoid of "action elements". Without elaborating on the various definitions of mediation I will try to show in this study that the Hegelian concept of mediation is action-oriented and, therefore, a biological-technical interpretation is possible.

If the philosophical-logical concept of mediation by Hegel is to be applied to biological or technical processes, then the cybernetic principle of feasibility enters the discussion. Specifically, the question to be posed is how different programs should be combined in order to supply operational instructions for a joint product. A further criterion to be considered is time since mediation is a process taking place within defined time scales. From a biological perspective living systems develop both within a circumscribed ontogenetic space of time and within an open (unlimited) evolutive space of time [19]. Mediation, thus, represents dialectic between the ontogenetic and evolutive realizability of programs.

In his *Phenomenology of Spirit* Hegel describes mediation as follows: "Mediation simply stands for a moving self-identity or reflection in itself...reduced to its pure abstraction, the pure essence" [4]. What does "a moving self-identity" mean from the perspective of feasibility? By mediation, Hegel understands a process (motion) and self-identity. Formally stated this refers to programs that are comparable to each other because of their isomorphic structure. An isomorphism is a bijective "structure-preserving" mapping from one abstract object to another. "Structure-preserving" means that some specific properties of, and relations between, the elements of an object (those which have been singled out as relevant for some reason) are preserved under the mapping. This formal mapping process could also be interpreted as "reflection in itself".

However, under the biotechnical criterion of feasibility, the concept of isomorphism is too weak, because the question must be asked which isomorphic programs are realizable within a given time scale. Here the principle of "spatio-temporal-equipotentiality of programs" is useful. At a given point of time during ontogenesis one specific program can be realizable, but a completely dif-

ferent one at some other time during the evolution of the system. Hence, mediation between realizable and non-realizable programs is "reduced to its pure abstraction, the pure essence", because non-realizable programs have to be rejected. If non-realizable programs are not rejected, they "feign" realizablility such that the program structure of the system is disturbed and either does not function at all or it generates "chimeric" products.

For a better understanding of my interpretation of mediation, I would like to refer to the example of the structure and protein producing function of a gene. Most genes of higher living beings are constructed such that protein coding sequences (exons) alternate with non-protein coding sequences (introns). However, the chemical structure of nucleotides that make up exons and introns is the same, rendering them isomorphic even though with respect to the realizability of their genetic coding they are different. The genetic code of the exons is realizable since it leads to a production of proteins. The genetic code within the intronic sequences is not realizable since it does not supply instruction for the production of a protein. Introns are therefore spliced out of mRNA shortly after mRNA synthesis. Importantly, introns also have a profound purpose. They serve as the hot spots for recombination in the formation of new combinations of exons generating novel protein isoforms [20].

For a long time, introns were regarded as worthless "evolutionary junk", which had to be spliced out from the gene. However, it is increasingly being stated that introns could harbor an evolutionary potential [21] [22]. Supposing that exons and introns are equipotential at least in terms of their principal coding function, the essential difference could be the fact that their "coding potency" is expressed at different stages during the evolution of a system. In other words since the introns cannot realize their potential coding ability during ontogenesis of a system, they have to be spliced out. Theoretically speaking this means the rejection of non-realizable programs. Under the perspective of spatio-temporal realizability of system programs, mediation thus means rejection. In this context it should be mentioned that Gunther [23]—in my opinion, the greatest philosopher of cybernetics—has introduced the rejection operator into formal logic characterizing rejection as an "index of subjectivity".

Let us return to Hegel once more. According to Hegel, mediation not only means "a moving self-identity", but also a "determination of the inner self by means of empty abstractions...it disappears into itself to the point of immediacy, where the inner and outer reality are identical and their difference is merely the act of determination or setting. This identity is the reality" [5]. According to my interpretation of mediation at the molecular level, this quotation from Hegel could be transferred to the molecular splicing mechanism used to generate the mature messenger RNA required for protein synthesis. In order to make this connection of ideas, I first propose that the word "abstraction" connotes rejection. The splicing mechanism would accordingly be an "abstraction of emptiness", *i.e.* a rejection of non-coding introns which are empty of useful genetic information for the organism at a particular point in the evolution of the species.

Introns are interspersed between the exons and at the same time, they represent the "empty interior" of a gene. Due to the splicing mechanism, introns turn to "immediacy" in the sense of non-mediation. One could also say that the expression of proteins made possible by the splicing mechanism represents a self-rejecting (intron abstracting) self-mediation of the gene. As I have already pointed out, in chemical terms the exons and introns are identical. The difference probably lies in the time scale during which they can express their code as proteins. In the Hegelian language, the difference between the gene sequences merely refers to this temporal "setting". Their equipotentiality, therefore, turns to "reality" at different times in the evolution of the species. Subsequently, my hypothesis states that schizophrenia is caused by a disturbance in mediation in the sense of an extensive loss of rejection. Let me attempt to show what this means on the molecular and cellular levels.

3. Non-Splicing of Introns: Elementary Mechanism of the Molecular Etiology of Schizophrenia

When introns are not spliced from genes involved in neurotransmission, a variety of outcomes are possible, depending on the normal function of the affected gene. In some cases the production of transmitters is decreased, in other cases, the neurotransmitter receptor has intron encoded sequence elements and/or premature stop codons that do not allow for proper transmitter occupancy. Supposing that glia determine the efficacy of neurotransmitter functions and set spatiotemporal limits in neural circuits (boundary-setting function; [15]), the inhibitory function of glial cells can be interpreted as a rejection mechanism as well. The glia can be thought of as rejecting some of the signals transmitted between neurons. For example, GABA (gamma amino butyric acid)-ergic receptors on astrocytes perform this inhibitory, or boundary-setting and rejecting function in glial-neuronal interactions. If non-splicing of GABA receptor mRNA changes the structure of GABA receptors, they cannot be occupied by GABA-transmitters appropriately and the inhibitory or rejection function of GABA is disturbed or lost [24]. Depending on the brain areas affected by mutations in the splicing controlling genes, a "borderless" generalization of functional units (neuronal groups) [25] results in the inability to reject information on the behavioral level. Therefore, the boundary between the brain and its environment is also lost [26].

The inability to reject non-realizable or "intronic" ideas may result in delusions and hallucinations and could explain why schizophrenic patients are unable to test the reality of their ideas and are at times absolutely convinced that all which occurs in their brains is real. In other words, the basic flaw that results in delusions and hallucinations is the loss of the capability to reject impossibilities concerning the realization of ideas in the environment. What is possible and what is impossible depends on the environment and thus changes with time. Therefore at a given stage in human evolution, certain ideas will be impossible to

realize and will be considered pathological, however, these same ideas may become realizable in the future, at which they will not be considered pathological.

4. Loss of the Glial Boundary Setting Function

Basically, glia have been shown to play an important role in modulating synaptic neurotransmission [27]. Glia divide the brain into compartments on the one hand, and create functional units in various time scales with the neurons, on the other hand. I have hypothesized that the glial networks have a boundary setting function in their interactions with the neuronal networks [15] [28]. Various experimental indications support the hypothesis that the glial-neuronal networks are organized in the form of domains as self-organizing units [16] [29]. According to Smolin [30] the setting of boundaries is an absolute prerequisite for a description of the universe. The universe can only be described if we set boundaries around regions and describe what is inside in terms of information that is associated with each boundary, Steindler [31] characterizes glial boundaries in the developing brain as "cordons."

Most neurotransmitter receptors and re-uptake systems for the transmitters have been detected in astrocytes including those for glutamate and GABA, the most abundant neurotransmitters in the brain mediating excitation and inhibition respectively. Neurotransmitters released mainly at the presynaptic terminal can activate different types of receptors on the postsynaptic membrane and specific receptors expressed by glial cells [32].

If non-splicing changes the structure of glial receptors, then the receptors cannot be occupied appropriately by their transmitter ligands so that the modulatory function of synaptic transmission by glial cells is disturbed or lost. Therefore, the negative feedback loops between neuronal and glial systems are interrupted. It makes no difference if an excitatory or an inhibitory transmitter system is affected. The point is that glial receptors cannot be occupied and that, at least locally, neuronal transmission cannot be interrupted. As a result, neither excitatory nor inhibitory transmitters are able to act in well defined spatio-temporal functional units in the brain. The type of imbalance of transmitter systems will depend on the brain area and the neuronal circuits affected.

Most recently, truncated neurotransmitter receptors have been identified in neurons of various regions in brains with schizophrenia [12]. However, truncated receptors in astrocytes still await their identification as far as brains with schizophrenia are concerned. Importantly, truncated isoforms of tyrosine receptor kinase B are found in astrocytes in relation to injury-induced neuropathic pain [13]. Of special interest are experiments on human glial chimeric mice using human glial progenitor cells demonstrating that the differentiation of astrocytes is delayed and astrocytes show abnormal morphologies. These experiments suggest that cell-autonomous gliopathology significantly contributes to the genesis and development of schizophrenia and supports the clinical observation of the onset of schizophrenia in adolescence [33]. Basically, schizophrenia is a

chronic and debilitating disorder characterized by a reduction in the number of astrocytes, accompanied by failure of their homeostatic function, especially glutamate homeostasis [34]. The further elaboration of the synaptic pathophysiology is not within the scope of the present study (for review see [35]).

Admittedly, it can be argued that there are diseases caused by genetic changes in neurotransmitter receptors which still do not produce schizophrenic symptoms for instance in congenital myasthenic syndromes that are due to mutations in acetylcholine receptors [36]. Schizophrenia will only occur if the following conditions are met:

1) The functions of rejection and boundary setting with respect to the environment that glial cells perform in the brain must be severely disturbed or lost due to mutations in genes that control splicing. These genetic lesions affect not only molecular and cellular processes but also the psychobiological behavior of the individual (see next section).

2) Stressors (life events, object loss, organic disorders, viral infections, etc.) must occur to trigger schizophrenic symptoms in the genetically vulnerable individual (equifinal model of schizophrenia [37]).

5. Explanatory Model of Schizophrenic Symptoms and Behavior

The phenomenology of schizophrenia is multi-fold. My hypothesis attempts to explain the multiple symptoms of schizophrenia in terms of loss of ego or self boundaries [38] [39] [40]. As already discussed, mutations in the genes that control splicing may result in a "borderless generalization of functional units" causing an incapacity to reject information on the behavioral level. Therefore the patient is unable to test the reality of his(her) ideas.

We should first assume that the ability of the human brain to develop new ideas is nearly unlimited. For example, in the dream state our brains produce scenes that are not realizable during waking. Man is only able to fly in his dreams. If a schizophrenic patient states that he has just been flying, to him this scene produced by his brain has really taken place because he cannot differentiate between his inner world and the outer world. Therefore, everything taking place in the brains of schizophrenic patients is reality as far as they are concerned. There is a loss of the capacity to accept information that contradicts the ability to fly and to reject the delusion as a consequence.

Hallucinations are caused by the same disorder. If a patient hears the voice of God giving him commands, then he must obey because he is convinced that the voice belongs to God. The patient is in no way accessible to the argument that God did not give the command, because he cannot distinguish between his inner and outer reality. The loss of ego boundaries is also evident in the content of delusions. For example, one of my patients is absolutely convinced that he is simultaneously Ceasar, Napoleon, Churchill and "Urbi". "Urbi" is a schizophrenic neologism, that is a novel verbal construction that has a mysterious meaning

only to the patient.

If a patient believes he is God and the Devil in one person, to an observer this might appear as a split mind and thus schizophrenic. However, I interpret this delusion as a loss of ego boundaries, since the patient is unable to distinguish between God and the Devil. We are dealing with a logical generalization [41] [42] in the sense of holism. Accordingly, I have proposed that schizophrenia primarily characterized by the symptoms of hallucinations and delusions should be designated "holophrenia" [41].

Delusions and hallucinations are "phenomena of intense self-consciousness and alienation", pointedly characterized by Sass [43] as "hyperreflexivity". My hypothesis could explain why the subjective reality of schizophrenic patients appears contradictory to the observer. There are for example patients which experience themselves simultaneously as omnipotent and extremely stupid. These two seemingly contradictory self images of omnipotency and impotency are often observed in schizophrenia. However, this apparent contradiction is solved as soon as the criteria of feasibility and the temporal conceptions of ontogenesis and evolution are introduced. Hyperreflexivity may arise when the patient is aware of his(her) evolutive potential but at the same time realizes its non-realizability within his ontogenesis. Sass [43] describes this experience of reality impressively in one of his patients: "it seems that Natalija existed in a kind of fitful equivocation between objectification of the self and subjectification of the world, between self-abrogation and self-deification, between a sense of finitude and of the infinite". Depending on the brain areas affected, the loss of the boundary setting function and the corresponding generalization of brain functions may show up in the motor, affective, or cognitive behavior of the patient. For instance, catatonic agitation, in which a disinhibited discharge of nearly all motor systems occurs, is an expression of motor generalization with raging and screaming as behavioral components. Here we are probably dealing with an excess in excitatory transmitter systems. If a catatonic stupor occurs, which implicates a state of complete motor inhibition, presumably the inhibitory transmitter systems predominate.

Affective flattening is regarded as a negative schizophrenic symptom showing a lack of emotions characterized by an apathetic facial expression and little or no change in the strength, tone of voice [1]. This symptom can also be explained as a loss of boundary setting. The different affective or emotional qualities cannot be produced within the brain and the communication of feelings is disturbed as a result. This dysfunction specifically affects the limbic system. Dysfunction of thought in schizophrenic patients appears as an incoherence (loss of meaning) of thought processes. Since the contents cannot be distinguished with respect to their qualitative independence, the patient is unable to meaningfully sort his(her) thoughts or to reject meaningless ideas.

The loss of spatial boundary function can also appear as megalomania. For example, one patient said: "I am the universe". Another patient recently stated:

"I am eternity. Do you now realize how much I am suffering?" In the latter case there is obviously a loss of the temporal boundary setting function. One could call it a "delusion of eternity". Many schizophrenics experience their reality as uncanny [44], they have a feeling that they are not able to fulfill a program determined by almighty forces. Here my molecular hypothesis may offer an explanatory model. Could these unrealized programs be compared to introns? Perhaps these programs are not yet realizable because they have occurred too early in human evolution. In an analogous fashion, introns that are not appropriate for encoding protein sequence now may serve this function quite well in the future. Similar to the thoughts of a schizophrenic patient, one can designate an intron encoded protein sequence as being "strange".

I started out from a philosophical perspective stating that schizophrenia may be caused by a disorder of mediation in the sense of an extensive loss of the function of rejection. Therefore I would now like to report on a patient who is suffering from this "mediation disorder", albeit he has got a creative solution to this problem. He is convinced that he can bring paradise to mankind. He can even define what he means by paradise: "in paradise the bodies of man and woman are so close together that nothing can divide them, no plants and no animals". This patient has described the final state of mediation processes, where all evolutive programs have achieved their "paradisian" goal and, thus, they can be rejected. Could we learn from this patient what mediation really means?

6. Delusional Robots

Although my hypothesis can be tested on the molecular level, its testing on the cellular level is limited. Neurobiology produces more and more data and seems to be stuck because it works on inadequate theoretical premises like the Turing computation. One way to cope with this dilemma is the construction of robots whose behavior could teach us what is going on in the brains of their creators [45] [46]. How could a robot be constructed in order to demonstrate schizophrenic or delusional behavior?

First, the robot brain should be equipped with many operational instructions (instructions on how to execute a program). The robot must then test if these instructions are realizable. The realizability depends upon whether the robot is mechanically equipped to execute operational instructions in the first place, or if the environmental situation at a given point in time is incompatible with the realization of a specific operation. With support of his perceptual and motor systems the robot should then test the individual operational instructions of each "working program" with respect to their realizability.

Operational instructions that are not realizable must be rejected ("spliced out") so that the program exclusively consists of realizable instructions. This procedure corresponds to the molecular splicing mechanism which plays a decisive role in my schizophrenia hypothesis. Specifically, if the robot fails to reject non-realizable ("intronic") instructions, he behaves as if all of the operational

instructions of his program are realizable and suffers from delusions as a consequence.

A robot that behaves as if a set of his operational instructions are realizable, when in fact they are not, is basically a "delusional robot". The observer would recognize the "insanity" of the robot by its behavior. For instance, if a humanoid robot failed to reject the operational instruction to fly, then it may suddenly start waving its arms like a bird when instructed to fly. However, this instruction is non-realizable, because the robot is not constructed to fly and its absurd attempt to fly would be seen by the observer as delusional behavior. Another example would be a robot marching through a desert who is given the command to start swimming. If this non-realizable program is not rejected, then the robot may lie face down and with his arms and legs start making what appear to be swimming strokes. Such behavior, which is completely out of place under the circumstances, would be interpreted as madness.

Accordingly, a robot must be able to reject non-realizable commands in a working program in order to function well in the environment in which it finds itself. In contrast, a robot that is programmed so that all commands have to be executed, or a robot having a technical defect that disrupts the rejection mechanism will not function well in its environment. These disorders in the action program of the robot are comparable to "non-splicing" of introns and "chimeric" receptors on the neurons or glial cells. The non-rejection of non-realizable commands in a working program corresponds to the "intronic ideas" of schizophrenic patients, and the inefficient behavior of the robot can be compared to the "chimeric" receptors on glial cells which cannot be occupied with the appropriate neurotransmitters.

In a more philosophical language, one can say that a delusional robot cannot mediate between intentional programs and their realisability in this environment. According to Chella [47] the issue of robot experience is one of the main challenges in the field of robot consciousness. Supposing that schizophrenia is a disorder of consciousness caused by pathophysiological mechanisms in glial-neuronal synapses [48] then to build robots that show forms of delusional experience may inspire the building of humanoid robots [35].

7. Conclusion: "Too Soon on Earth"

I started out with the notion that mediation is an operation that rejects non-realizable programs, such as ideas and desires, and which plays a decisive role in complex systems. Intentional programs during ontogenesis of a living system that are not realizable at the present time may at some future stage of evolution become optimal and realizable. Though intron retention also exerts a high combinatorial power for protein production, in the present study, I focus on non-splicing resulting in truncated chimeric proteins. Basically, the structure of exon-intron protein-coding genes appears to have evolved concomitantly with the eukaryotic cell, and introns were a major factor of evolution throughout the

history of eukaryotes [49].

Aside from molecular-biological and neurobiological consequences disclosed by my explanatory model of schizophrenia, this model may also yield a better understanding of the conscious state of those fascinating and pitiable patients suffering from schizophrenia, which would be of special importance. Are they aware of the "intronic potency" of our genome, since they have this non-rejected code at their disposal? Do these patients suffer from the non-realizability of their programs (wishes, desires, ideas)? Does insanity mean that they are aware of evolutionary potencies making them believe to be omnipotent and at the same time increasingly losing their social abilities? One patient once said to me: "Doctor, I am the Almighty God, but I am hungry, please give me some money. I know 'now' why I am hungry, the Devil has put me on earth too soon."

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Conflicts of Interest

The author has declared that no competing interests exist.

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