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Alzheimer's Disease Illuminated: An Information Processing Point of View and Perspective

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Abstract

Alzheimer's disease (AD) is a dangerous degenerative disease that affects the central nervous system of elderly people. In recent years, it has become a serious problem facing the modern society. Since the causes of the occurrence and spread of AD are still unknown, scientific research in these matters is of exceptional importance. Its main efforts are directed at the investigation of the mechanisms of the disease's onset and progression. Among the mechanisms being researched are genetic, epigenetic, molecular, and environmental mechanisms. For unexplainable reasons, this list does not include and does not even mention information processing mechanisms. Why? Information processing is the bulk of brain activity. That is a generally accepted and indisputable frame of mind! The only possible explanation for such a slip can be only one: contemporary neuroscience (neurobiology) knows nothing about what information is and what information processing stands for! The purpose of this article is to correct somehow and perhaps improve this incredible situation.

Introduction

In late January 2024, news spread all over the world that Biogen had stopped further development of the drug Aduhelm, a drug that was intended for the treatment of Alzheimer's disease (AD), [1-5]. This was the first drug in 17 years, that was (so it was announced) capable of treating Alzheimer's disease, and which had already received The US Food and Drug Administration approval in June 2021 [1, 5].

Aduhelm was declared as a groundbreaking discovery that would pave the way for a new class of drugs and reinvigorated investments in the field [1]. However, it turned out that the victorious reports were somewhat premature, and the healing qualities of Aduhelm were somewhat exaggerated.

Alzheimer's disease is an incurable and unpreventable disease that affects the central nervous system of elderly people. The number of AD involved in the world is estimated today at 55 million people. This number is expected to increase to 78 million by 2030, and to 139 million by 2050 [6].

Due to the high frequency and severity of the disease, AD is becoming a significant medical and socio-economic problem in the modern world. Huge financial resources are allocated by the budgets of different countries to solve the problems that accompany the rapid spread of AD.

In the US, financial costs directly related to Alzheimer's disease were $321 billion in 2021. And the indirect costs (associated with home caregiving services) are estimated at $272 billion [7]. The total spending (321 + 272 = 593 billion) is comparable to the US military and defense spending – $778.40 billion in the 2020 budget [8].

It is generally agreed and accepted that the severity of the social and economic burden that AD places on modern society is further aggravated by the fact that, despite the almost 120-year history of confronting this disease, humanity knows almost nothing about the causes of its onset and the paths of its development. To reduce the severity of this burden, a network of research institutions and establishments was created and launched aimed at changing the existing state of affairs. The budget of one of the largest organizations funding research and study of AD (the American National Institutes of Health) in 2017 amounted to $1.4 billion (the total budget of NIH in 2022 was $45 billion) [9].

For a better understanding of what are the causes of AD and what are its underlying mechanisms, a large amount of scientific research is focused on developing disease models (direct studies of the human brain are prohibited). Models are developed based on biological mechanisms taken from various fields of knowledge, such as genetics, epigenetics, molecular biology, neural

and environmental behavior traces. There are 172 research trials running today in various research institutions addressing a wide variety of biological processes involved in AD [10].

However, looking at the list of current studies, you suddenly notice that there is nothing on this list about the brain's information processing modeling! How can this be?! It is generally agreed and accepted that **the balk of the brain's activity is information processing.** (Try to inquire Google with the statement "Brain is processing information" – Chrome Google returns 10,300 results, Scholar Google 288 results, and Microsoft Google 29 results. A convincing response that nobody is unable to argue with). Therefore, it is only natural to see the source of brain disorders in the impairments of brain information processing activity.

I am not a doctor, not a microbiologist, not a neuroscientist, not an AD researcher. I am an engineer who once was engaged in problems of Computer Vision, Robotics, and Artificial Intelligence. Via this R&D involvement, I was confronted with problems of human brain functioning. The main lesson that I kept from this my engineering experience was that the working brain is busy with information processing.

Therefore, it was a great surprise to me that the study about mechanisms and causes of brain disorders does not pay any attention to brain information processing mechanisms!!! Why? How such an important feature of brain activity can be overlooked and disregarded in AD investigations?!

My answer to this question is only one – the AD research community does not have the slightest notion about what information is and what information processing is supposed to be for.

In this regard, I will try to close the gap and to explain the AD research community what they have to know about these just-mentioned topics. I hope, that this new knowledge will critically advance and accelerate AD research investigations.

The First Step – What is Information?

We live in the Information Age, and today the most commonly used word is "information".

However, despite its widespread use, a consensus definition of Information does not exist.

The concept of "information" was first introduced by Shannon in his seminal 1948 paper "A Mathematical Theory of Communication". Then later other scientists joined the venture – Kolmogorov, Fisher, Chaitin, and others (see [11, 12, 13] and references therein). However, none of them did not try to define what is "information". They were busy with the "measure of information". That was enough to improve the performance and reliability of technical communication systems. At the same time, the meaning of the transmitted message, and its semantic features were completely ignored.

In modern sciences, and especially in biology, the needs of communication cannot be reduced only to the optimization of the technical parameters of the communication system. The semantic aspects of the message are of a paramount importance, and thus must be met.

Following the soul and spirit of this requirement, I have developed my own definition of information. (Interested readers can look into the references [11, 12, 13]).

My Definition of Information Sounds Today Like this:
"Information is a Linguistic Description of Structures Observable in a Given Data Set."
As it was already mentioned, my background is in Computer Vision and Image Processing. Thus, I will use known to me and drawn from these fields examples to make my explanations of the information definition more palpable and clearer.

So, let us take a digital image as a given data set. A digital image is a two-dimensional set of elementary data points called picture elements or pixels. In the image, the pixels are not randomly distributed, but due to the similarity of their physical properties, they are naturally grouped into some kind of bands or clusters. I propose to call these clusters **primary or physical data structures**.

In the eyes of an external observer, these primary data structures are arranged into larger and more complex agglomerations, which I propose to call **secondary data structures**. (Which are essentially structures of structures, complex structures composed from more simple ones).

These secondary structures reflect the observer's view of the grouping of primary (or lower level of complexity) data structures, and therefore they could be called **meaningful or semantic data structures**.

While the formation of primary (physical) data structures is determined by **the objective (natural, physical) properties of the data**, the subsequent formation of secondary (semantic) data structures is **a subjective process governed by the conventions and habits of the observer** (or a mutual agreement of an observers' group).

As said, t**he description of structures observed in the data set should be called "Information"**.

In this regard, it is necessary to distinguish between two types of information – **physical information and semantic information**.

Both are language descriptions; however, physical information can be described using a variety of languages (recall that mathematics is also a language), and semantic information can be described only using the observer's natural language. (See [12] for more details).

An important consequence of the above definition of information is the understanding that **information descriptions always materialize as a set of words**, a fragment of text, a narrative. In this regard, an important note should be made – in biological systems, **these text sequences are written with nucleotide letters and amino acid signs**, (some evidence of this see in [14]).

This turns the information into a physical entity, into a "thing", [15]. With its weight, length, and other physical prop-

erties. For the purposes of our discussion, this is an extremely important remark.

The Second Step – Information Processing and Information Flow

I deliberately outline at such length and detail the innovations that follow from the new definition of "What is information", because the new definition of information radically changes our understanding of what **the route of information processing** (in the human brain) is and what is hidden in the advancement of processed information within a chain of neurons that is called "**information flow**".

Because, if we want to understand what "**brain disorders**" are, we must first of all clarify what the "brain order" (the right arrangement of things in the brain) is. This is the most important question in contemporary neuroscience.

And even before that, it would be worth to understand **what the brain is in general**.

Understanding what the brain is in general, begins with the works of **Santiago Ramon y Cajal** of Spain, carried out in 1888-1896, and called "**The neuron doctrine**", [16, 17]. According to this doctrine, the brain consists of many individual nervous units (neurons) that have no anatomical connection with each other. Each distinct neuron consists of three parts: a nerve cell (soma), a nerve fiber (axon), and terminal branches (dendrites). The axon of one neuron connects to the dendrites of another neuron through a synapse. Synapses take part in the transmission of signals (nerve impulses) that neurons exchange with each other. Nerve impulses are transmitted by contact, as connected electrical conductors, or by a kind of induction, as when using induction coils [18].

The understanding that neurons interact by transmitting electrical impulses (Santiago Ramon y Cajal, Nobel Prize 1906, [16]) was further developed by the work of Hodgkin and Huxley, who turned an anonymous electrical impulse into an **action potential**, propagating along the axon from the body of the neuron (soma) to the synapse, connecting the axon to the dendrite of another neuron. (Hodgkin and Huxley, Nobel Prize 1963, [19]).

Although, throughout the century, the main type of communication between neurons was considered to be in the form of electrical (action potential) impulses (Hodgkin and Huxley, Nobel Prize 1963 [20]), along with it, ideas arose about communication in the form of chemical neurotransmitters (Henry Dale and Otto Loewi, Nobel Prize 1936, [21]) or in the form of a flow of ions (Erwin Neher and Bert Sakmann, Nobel Prize 1991, [22]).

Although, throughout the century, the forms of interneuron communication have constantly changed, what exactly is being transmitted from neuron to neuron in the neural communication chain (information flow) has invariably remained outside the researchers' field of view.

The concept of "Information" (in the form of Shannon information, [13]) appears only in the late 40s. Neither Shannon nor his followers have ever defined what "Information" is (They were busy with "information measure" evaluation). Despite of this, the terms Information and Information Processing have become very common and popular in brain research, [23-25].

20 years ago, I proposed (to the community of Computer vision and Image processing) my definition of information, which differs from the generally accepted one (that, which is inspired by Shannon's 1948 article). However, my community guys showed no interest in my proposal [13]. Now I am trying to offer my definition of Information to the community of neuroscientists and medical professionals, to those who are busy with the problems of Alzheimer's disease, and brain disorders, in general.

As mentioned above, in my opinion, information is a linguistic description of structures (of data) that can be distinguished in a given data set. What follows from this is that information (especially in biology) is shaped as text strings (describing the structures), written in some biological language with biological letters (nucleotides and amino acid signs). Therefore, these informational records are truly real – that is, they have weight, length, and some other physical properties.

The first, initial level descriptions of the simplest structures are called by me "physical information". From the initial (primary, physical) structures, the observer conceives (in his head, in the brain) more complex secondary structures. We could call them "structures of structures"; and their descriptions may be called "semantic information". Undeniably, all these information descriptions are material, substantial, real.

Although my definition of information is very different from the traditional one (supported by the fame of the four Nobel Prizes), they are not completely groundless and are confirmed by numerous new scientific observations. Electrical Action potential is today associated with material cargo vesicles, which move along the axon, and upon reaching the terminal end, they disintegrate into many sub-parts, which today are called neurotransmitters [26, 27]. (The doubtful transition of the electrical impulse into chemical neurotransmitters is also no longer needed today).

All this is radically different from what classical sciences understand by information. All this radically changes the picture of what is today called "information flow" and "information processing."

The classic problem of the interrelation between primary information (usually called "syntactic" information) and secondary, "semantic" information, simply disappears when my definition of information is being used – syntactic (in my definition "physical information") and semantic information are simply descriptions of structures of **different levels of complexity** [37]. What we call "information processing" is the process of creating new structures of varying (increasing) complexity (and, self-understandingly, creating their descriptions,). This is exactly how information is processed in a subject's head, in his brain.

Armed with this understanding of "what is information" and "what information processing is", we can now move on to the discussion about what "brain disorders" or "brain dysfunctions" are.

The Third Step – Information Processing and Alzheimer

It is generally agreed that Alzheimer's disease (AD) is associated with uncontrolled accumulation of organic debris that ap-

pear in the cellular and intercellular spaces during brain function. Known examples of these debris are beta-amyloids and tau threads [34]. But there are also other proteins whose presence is not so noticeable. All medical efforts aimed at combating AD to this day are focused specifically on the fight against beta-amyloids. (The scandal with the new drug being developed by Biogen, which was mentioned in the Introduction, belongs precisely to this class of beta-amyloid struggling).

How and why beta-amyloids appear in the brain nerve cells? – science knows nothing about this yet. And therefore, all efforts are aimed not at eliminating the causes of the amyloids appearance, but simply at combating their appearance as such. This, in my opinion, is the reason for the failures of Biogen and all other developers of AD treatment drugs [2].

The fight against the appearance and presence of amyloids simply comes down to their removal. And this is certainly not a solution to the problem – you remove these ones; new ones will immediately appear.

What does this problem look like from an information processing point of view? No one can deny the appearance of debris during the activity of a nerve cell. It is quite reasonable to assume that something similar happens also in the course of cell information processing.

As mentioned above, when processing information (semantic information, because it is the semantic information that is mainly being processed in the brain), lower-level information structures received at the input of the neuron are reorganized into a structure of a higher level (a higher level of complexity). And all this reorganization is not carried out randomly, but in accordance with a template (prototype), which is stored in the neuron's memory (precisely for these purposes). In this case, we are talking (and this has already been mentioned above) about the processing of texts, records made with nucleotides and amino acid signs. (Because this is exactly what, according to my information theory, semantic information and its processing in the human brain looks like).

It is clear that when texts are being processed, processing waste appears instantaneously – not all fragments of texts are being processed, because some of them do not correspond to the prototype example that is stored in the neuron's memory. On the other hand, fragments of processed texts do appear as a result of semantic information processing, (which is text rearrangement into a new structure).

All this falls under the definition of "information garbage" (which is not much different from the garbage that, according to the current view on neuron activity is generated at the neuron, [28]), without recognizing or mentioning semantic information. And this garbage is usually removed from the cell and is further processed, for reuse or for being subsequently removed from the system.

The introduction of the concept of "information garbage" makes clear the reasons for its occurrence (formation) as well as the ways to combat its accumulation, (which usually leads to loss of brain performance, its degradation, and degeneration) [29].

From this immediately arise the conclusions that must be made to eliminate the problems associated with the uncontrolled accumulation of organic debris in the nerve cell:

- First, (and this is very important) the appearance of garbage is a natural process, and it cannot and should not be fought against.
- Second, the removal and disposal of waste is carried out under the control of genetic mechanisms that nature created specifically for these purposes. Disruption of these genetic mechanisms causes debris accumulation (first inside the cell, and then in the intercellular space).
- Third, to restore the natural order of waste removal, the genetic mechanisms and genes responsible for these processes (disordered for some reason) must be restored. Today this is already a solvable problem; today there are CRISPR technologies for this [30, 31].
- Fourth, the fight against the formation of amyloid clusters in the intercellular space is an erroneous and senseless direction of work in the domain of AD research.

More about AD and Information Processing

There is a belief that early detection of Alzheimer's disease leads to more successful treatment. For the purpose of this early detection, a system of biological markers for AD has been proposed and developed (and successfully applied).

As is known, the processing of information waste occurs in several stages – garbage removed from the neuron cell (from the different parts of it where information processing actually takes place – from the dendrites, from the soma, from the axon, from the synapse) into the inter-neuronal space (usually filled by glia), where the garbage is further processed and then discarded into the blood. With the blood, the garbage enters the liver. From the liver – into the urine (and possibly into feces), and in such a way it is finally removed from the body.

We are interested in these details of garbage removal (from the cell body) because, at the stage of transporting the garbage in the blood, the amount of garbage in the blood can serve as an indicator of the disease's presence and its development stage. This is already used today as a way to identify and assess the state and the stage of the disease based on the presence of specific biomarkers of the diseases in the blood (i.e., in the AD practice there is already a pursuit for specific pieces of garbage that indicate the state of the disease, [32-34]).

But in the case of an informational approach to AD problems, the presence of certain biomarkers by itself does not say to us nothing – information garbage is always present in the subject's blood, because information garbage is a natural by-product of information processing. As an indicator of the disease must be considered the **change (increase or decrease) in the level of information garbage in the blood**.

An increased level of information garbage in the blood indicates a possible dysfunction of the cleaning mechanism, when the cleaning mechanism does not distinguish garbage from useful information. And it destroys the epigenetic memory (which is the information prototype stored in the semantic information processing system). The loss or partial impairment of this memory leads to degeneration of the system. (For example, various

forms of sclerosis). An increased level of information junk in the blood, therefore, indicates precisely **this dysfunction of information processing – the destruction of epigenetic memory**.

A decrease in the level of information garbage indicates that the mechanism for removing garbage from the neuron is damaged, that is, the garbage is not removed and remains in various places in the neuron cell, **clogging and interrupting the normal system's information flow**, stopping the flow of information in the system.

An informational approach to the functioning of the brain allows us to take a fresh look at the variety of forms of degenerative diseases (disorders) that exist today. The need to remove information debris from a nerve cell (from all of its components) is common to all brain cells. But the cells themselves have different functional dedications. Therefore, disruption of their work (in the case of information garbage creation or removal) looks different in different cells. And historically, this has led to different names for the same phenomenon in different functionally oriented cells. That's why we have today a whole spectrum of dementias – Alzheimer's Disease, Parkinson's Disease, Dementia with Lewy Bodies, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia, and Huntington's Disease.

Misunderstandings about the nature of AD often lead to erroneous recommendations for the caregivers of AD patients (or patients with other dementias).

There is another legend about the features of AD, which is impossible to negate without the help of an informational approach to AD. We are talking about the recent widespread stories that targeted interventions in people's daily routines can lead to improvements in their impaired cognitive abilities. Interventions such as nutrition, exercise, and stress reduction are assumed. The effect of physical exercises on restoring cognitive deficits is considered particularly successful.

However, several studies of such interventions indicate a very limited effect on improving the cognitive abilities of subjects [35]. There is no normal theoretical justification for such an intervention at all. I'll try to do this below.

As is known, AD leads to the death of neurons. However, it is known that nature compensates for the constant loss of neurons through the birth of new neurons. This is called neurogenesis, and occurs in the brain constantly throughout a person's life. New neurons are thought to replace dead neurons. But this replacement is incomplete. In new neurons, in their nucleus, DNA (common to all cells of a given organism) is always delivered, thus providing the new neuron with the genetic memory (memory received from ancestors, from parents). However, the new neuron is devoid of the epigenetic memory (memory that a person accumulates independently throughout his life).

As you know, to process semantic information, a neuron requires a prototypical memory, which includes physical information (genetic memory) and semantic information (epigenetic memory). The neuron always has the genetic memory – it is obtained from the DNA that every cell poses from the moment of its birth. However, the newborn neuron does not have the epigenetic memory, which is usually acquired during the whole lifetime. Only a small part of it can be recreated through new life experiences that come with regularly repeated physical exercise (in the form of daily walking, for example), with repeated limited complexity cognitive problem solving (in the form of crosswords or puzzles), and repeated social interactions. This is a very limited life experience, and a very limited epigenetic information recovered, but it is enough to improve the AD patient's self-perception and mood, to improve his limited everyday activity in the limited world surrounding him.

In this case, restoration of the lost epigenetic memory does not occur. A very narrow, limited volume of new epigenetic memory is acquired, which is mistakenly interpreted as an improvement in cognitive abilities. But this is an illusion, this is not the so anticipated remedy.

Some Concluding Remarks

The main purpose of this article was to introduce the community of biologists and medical professionals to the new and unknown (to them) concepts of "information" and "information processing". It seems to me that I successfully carried out this task. Relying on these new concepts of information and brain information processing, I was able to explain the previously unclear principles of Alzheimer's disease onset and development.

The concepts of physical and semantic information, which I derive from the definition of information as a linguistic description of data structures visible in a given set (of data), are very important innovations that previously were unknown to biological scientists (as well as to all other scientists). Today, many scientific disciplines (mainly technical) are devoid of semantic information comprehension and promise to remain in this state further in the future. The father of modern Information Theory, Cloud Shannon, wrote in 1949: "These semantic aspects of communication are irrelevant to the engineering problem… It is important to emphasize, at the start, that we are not concerned with the meaning or the truth of messages; **semantics lies outside the scope of mathematical information theory**" [36].

This disdain for semantic information continues to these days. Even today, many sciences, that rely on and use information in their research, see "syntactic" or "data-driven" information (what I call "physical" information) as the only kind of information to be useful. Although they feel the need for semantic information (the life demands it), because they have no idea about what it is, they try to derive semantic information directly from available syntactic (physical) information. Well, well – **but this is pure alchemy!** Nevertheless – Bioinformatics, Computational Biology, Computational intelligence, Artificial intelligence, and many other sciences – are happy today to be engaged with this alchemy, reporting about new achievements, and being very proud of them.

It seems to me that I was lucky to convince my readers that another definition of information and, resulting from it, another definition of information processing is possible. And that these new definitions could be useful and appropriate when studying not only the peculiarities of AD, but also many other diseases, which could be described in terms of appropriate semantic information – endocrinological, oncological, hormonal, and other diseases are awaiting such opportunity.

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