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Alzheimer? But You Look For Answers under a Wrong Lamp Post

*Emanuel Diamant**

Independent Researcher, Israel

***Corresponding author:**

Emanuel Diamant

Independent Researcher, Israel
E-mail: emanl.245@gmail.com

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ABSTRACT

Alzheimer's disease (AD) is a dangerous degenerative disease affecting the central nervous system of people over 65 years of age. Today there are 55 million people in the world disturbed by AD. It is expected that by 2030 there will be 78 million, and by 2050 139 million. Due to the high frequency and severity of the disease, AD is becoming a significant medical and socio-economic problem of 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. Since the causes of rise and spread of AD are unknown, an important role is given to scientific research on the mechanisms and ways of AD commence and development.

I am not a doctor, not a microbiologist, not an AD researcher. I am an engineer who once was engaged in problems of Computer Vision, Robotics and Artificial Intelligence. In this way, I was connected with problems of human brain functioning. That explains my current interest in AD problems. Reviewing the literature, that is now available to me, about the mechanisms of AD onset and development, I was extremely surprised that among the variety of mechanisms that are currently studied in the United States (and around the world), informational mechanisms, mechanisms for exchange and processing information in the brain's neural networks are not considered at all, and even are not mentioned (in these studies). But the human brain, first of all, is a provision for information accumulating and processing! How can such a thing be neglected? In the note below, I try to explain the possible usage of informational models in AD problems and challenges.

INTRODUCTION

Dementia is a general term used to refer to a wide range of brain diseases that cause a decrease in a person's cognitive abilities (consciousness, thinking, memory, and other forms of cognitive activity). AD is one of the forms of dementia, the

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most common form - Alzheimer's disease accounts for 80% of the cases of dementia [1].

Alzheimer's disease (AD) is an incurable progressing brain disease, accompanied by devastating a person's basic cognitive functions and abilities (memory, thinking, attention, orientation, etc.).

Alzheimer's disease is one of the most severe and widespread disease today. The number of AD affected in the world is estimated at 55 million people. This number is expected to increase to 78 million by 2030 and 139 million by 2050 [2].

Alzheimer's disease today is an incurable disease with a fatal outcome. On average, a person with distinguished Alzheimer's disease lives 4 to 8 years after the diagnosis [1].

Official death certificates recorded 121,499 deaths from AD in 2019, the latest year for which data are available [3].

Due to the high frequency and severity of the disease, Alzheimer's disease is becoming a serious medical and socio-economic problem of the modern world, and its impact will steadily increase as the population ages. The rapid spread of Alzheimer's disease is becoming a matter of concern and alarm for the governments and public institutions of many developed countries, for their medical organizations, and for the general public as well. 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 [3]. The total spending (321 + 272 = 593 billion) is comparable to the US military and defense spending – $731.75 billion in the 2019 budget [4].

Although Alzheimer's disease was discovered and described as early as 1906, even today scientists still do not fully understand the causes and the paths of Alzheimer's disease development.

Today, Alzheimer's disease is at the forefront of biomedical research. The budget of one of the largest organizations funding research and study of Alzheimer's disease (the American National Institutes of Health) in 2017 amounted to $1.4 billion (the total budget of NIH in 2022 is $45 billion [5]).

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

It is extremely surprising that information processing mechanisms are never mentioned in this regard. It is generally accepted that the brain is busy with information processing. The interaction of a person with the outside world involves information processing in the human brain. Human's cognitive abilities are associated with the ability to process information. Then what is the reason for such unexpected ignorance and neglect?

A possible answer might be that the research community avoids using conceptual "information processing" because no one in the community knows what "information" is. Today this statement is not entirely true, because for several years there have been several publications defining what is "information" and what is "information processing"! [6,7].

Here and now, I am ready to share my knowledge about this subject with everyone who is ready to listen and to accept my explanations.

WHAT IS INFORMATION?

The concept of "information" was first introduced by Shannon in his seminal 1948 paper "A Mathematical Theory of Communication". The original goal of the theory was to solve a purely technical problem: to improve the performance of a communication system. Therefore, only the physical properties of the signal and the channel were taken into account. At the same time, the meaning of the transmitted message, its semantic features were completely ignored.

However, in biology, as in many other modern sciences, the semantic aspects of the message are of paramount importance. In this regard, there is a growing need for a clear and unambiguous distinction between the boundaries of Shannon's and semantic information.

In accordance with the spirit of this need, I decided to adopt Kolmogorov's approach to the definition of information. The reasons and consequences of this step (my own, my new definition of information) I have already been published on various instances - interested readers can view and inspect these publications in the bibliography attached below [7-9].

For the purposes of this paper, I will use some extended excerpts from these previously published articles. My readers should be aware that due to my many years of experience with computer vision design problems, my explanations (written at

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certain points of time) are based on image processing habits and practices. However, I do not see any drawback in this - I hope my readers are smart enough to generalize image processing paradigms to more general cases.

So, inspired by Kolmogorov's approach to information [9], my definition of information today sounds as follows:

"INFORMATION IS A LINGUISTIC DESCRIPTION OF THE STRUCTURES VISIBLE IN A GIVEN SET OF DATA"

To make an understanding of this new definition (of information) more palpable, I propose to consider a digital image as a given set of data. 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 clusters or groups. I propose to call these clusters primary or physical data structures.

In the eyes of an external observer, these primary data structures are further organized into larger and more complex agglomerations, which I propose to, call secondary data structures.

These secondary structures reflect the observer's view of the grouping of primary data structures, and so they can 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 observer's conventions and habits.

As said, the description of the 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), while semantic information can only be described using observer's natural language. (More on this subject can be found in [8]).

Those who reviewed the reference [8] will find that each informational description is a top-down hierarchy of descriptions from coarse to fine, representing different levels of description complexity (different levels of description details). The physical information hierarchy is located at the lowest level of the semantic hierarchy. The process of interpreting sensory data materializes as a process of extracting physical information from the input data, followed by an attempt to associate this physical information about the input data with the physical information already stored at the lowest level of the semantic hierarchy (in the memory of the system). If such an association is achieved, the input physical information becomes associated (through the physical information stored in the system) with a relevant linguistic term, with a word that places the physical information in the context of a phrase that provides its semantic interpretation. Thus, the input physical information is called by a corresponding linguistic label and is formed into a suitable language phrase (and further - into a story, legend, narrative), which gives the input physical information the desired meaning.

An important consequence of the above definition of information is the understanding that information descriptions are always reified as a set of words, a piece of text, a narrative. In this regard, an important footnote should be made - these text sequences are written with nucleotide letters and amino acid signs. This turns the information into a physical entity, into a "thing", with its weight, length and other physical properties. For the purposes of our discussion, this is an extremely important addition.

With these new definitions of information in mind, we can proceed to the revision of today's brain information processing issues.

INFORMATION FLOW AND BRAIN INFORMATION PROCESSING

It is generally agreed and accepted that the human brain is an exceptionally powerful information processing device. A Google Chrome inquiry for "Brain information processing" returns 62,000 results, enough to support the validity of the statement "The brain is processing information."

In one of my early publications, I devote a special chapter to this issue [8]. Therefore, to save time and space, it seems to me reasonable to repeat here only some selected fragments of this article.

So, let's get started: The brain is processing information. Neurons are the functional units that do this work. Despite their discrete structure, neurons are not separate functional units successful information processing requires close cooperation between partners. For this reason, neurons are connected in a network in which they communicate with each

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other, transmitting, exchanging, transferring - in a word, jointly processing information. This transition of information between interconnected (at different levels of organization) neurons even received a special brand name "Neural Information Flow" and became the subject of close study and research.

From the point of view of interneuronal communication, neurons can be considered as a chain in which two consecutive units are connected through a synaptic contact. Each individual neuron consists of three constituent parts: dendrites (input part), cell body or soma (main part) and axon (output part). Understanding the functional role of these neural parts and how information flows through them has been a major goal of neuroscience for much of the past century. However, for some reason, among the three parts facilitating the flow of information through the neuron chain, the axon part has been the most explored and studied.

Several long paragraphs (in the cited article) are devoted to the theory of axonal Action Potential Propagation - how sequences of action potentials encode and transmit information in the neural network arrangement of the brain. The emergence of the molecular communication hypothesis, which suggests that bioactive molecules (lipids, proteins, various RNA and even DNA) can be informational carriers in the case of interneuronal communication, which greatly destabilizes and threatens the principle of axonal action potential propagation.

The concept of the neural information flow, which is generally accepted today, assumes different forms of information presentation in different parts of the neural information flow chain. The input part (dendrites) is dominated by chemical neurotransmitters and flows of electric charges (ions). The accumulation of electrical potential and the emission of an action potential are characteristic of the somatic part. Propagation of an action potential in the axon and then again conversion of the action potential into chemical vesicles (at the terminal end of the axon) before being released into the synaptic cleft between neurons are all multiple forms of representing information in a single neuron.

This does not seem to me plausible. Nature is conservative, it is hard to believe that at different stages of one unit of information processing (dendritic input - soma - axon - axon terminal - synaptic cleft) one part of the path is realized as a molecular cargo package, and the other part works completely differently. For example, the axon package spikes represent the transfer of information in the axon. It seems absolutely incredible to me. The idea that information can be encoded in the form of large molecular structures (as suggested by the theory of molecular biological communication) seems to me much more reasonable and acceptable.

Thus, the idea proposed in this article that information always (at all stages of the information flow) appears as a materialized text string (written in letters of nucleotides and amino acids), and definitely as such it is being altered (processed) at all stages of information processing in the information flow. This idea seems to me a much more reasonable and plausible explanation of what happens to information in the information flow.

With all of this in mind, we can now move on to discussing the main body of this article, discussing what all this means for a better understanding of the onset and development of Alzheimer's disease.

ALZHEIMER'S DISEASE AND INFORMATION PROCESSING PROBLEMS

The primary information extracted from the flow of sensory data that entered the brain through the sense organs is subjected to further processing and transformations at different stages of the information flow. At the same time (as it was already described in Part 2), there is a gradual enlargement of the structures of semantic information (which came through the dendrites from neurons of a lower level) and their new descriptions, new information structures (of a higher level) are created. This process occurs only when there are already in existence prototypes for new structures in the system, which are stored in the system's memory, in every single neuron memory. But what if there is no prototype in the neuron's memory, according to which a new (higher level) structure could be created from the received descriptions (received information)? In this case, processing information (by this neuron) stops, and nothing comes to the next level of processing (the flow of information is interrupted, the Information Flow is broken).

What happens (in all the cases described above) with the information previously received at the neuron input? Yes, nothing happens. Remember what happens to your mailbox when for some reason you do not regularly collect your mail from it - your mailbox quickly becomes clogged and not functioning.

To keep the mailbox in a functional state, it must be regularly reviewed and cleaned. The same should happen with the

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neurons. And it is not surprising at all that nature has taken care of the creation and implementation of such an opportunity - the constant and continuous cleaning of the neuron from the accumulating debris. To do this, it has a special, genetically provided and genetically controlled mechanism - lysosomes and lysosomal functions. There may be other mechanisms designed for this purpose. I do not know, I am not an expert in genetic garbage-collecting machines.

But from the literature available to me, I know that such an accumulation of "garbage" (not used and not processed for further disposal of informational text chunks) occurs in all parts of the information flow in each specific neuron of each specific neural network - in dendrites, in the soma, in axon [10]. The literature describes the destruction of dendritic spines, swelling of axons, tightness and loss of mobility of functional elements within the soma. Ultimately, uncontrolled accumulation of debris leads to neuron dysfunction and death, [11].

This is what we observe later as a dysfunction of the nervous system, which we call "Dementia". Since different areas of the brain have different functional purposes, neuronal dysfunction in these areas manifests itself in different ways. Therefore, we have a whole range of dementias. Alzheimer's disease is just one of them (although the most common). However, summing up everything that has just been said, it is necessary to emphasize the main thing - the main cause, the primary source of all dementias is the dysfunction and death of neurons (in different areas of the brain), due to the uncontrolled accumulation of information "garbage" in different parts of the information flow in the neuron [12].

AFTERWARD

The introduction and widespread use of the concepts of "information", "information flow", "information waste" (or "information garbage") greatly advances us in understanding the possible ways to combat and treat Alzheimer's disease (and, by the way, all other dementias). As mentioned above, they all have a common nature: uncontrolled accumulation of information waste; therefore one treatment will be possible for all of them: stopping the accumulation of informational waste and eliminating previously accumulated waste, processing and utilizing it.

The fact that this is a genetically controlled process is also known. And what genes are responsible for processing garbage in the soma is also known. What genes are responsible for processing garbage in dendrites and axons is not yet known - no one, in fact, has looked there and searched for the causes of disturbances in the course of processing and disposal of garbage.

The ability to control and correct the work of these genes already exists - it is called genetic engineering. All its peculiarities are already known, the capabilities of genetic engineering have been recently demonstrated by the successful development and implementation of the COVID vaccine (see Google "Genetic engineering of the COVID vaccine").

While scientists are still gathering and learning to "repair" the genes responsible for the removal and utilization of informational garbage, some possibilities for alleviating the condition of patients affected by some other types of dementia are already being tested and implemented. Right, this is done intuitively, without a clear understanding of what, why, and how all this is being done. But in fact, behind their first success is this:

Stories that neurons in the brain are dying, and new ones do not appear instead, are stories, which have nothing to do with reality. There is such a thing as "neurogenesis", and in the brain, next to dead neurons, their newly-born relatives appear. There is, however, a significant difference between them - new neurons have only genetic memory (memory of the experience of our ancestors), and no epigenetic memory (memory that we have developed during our own lives). Therefore, when it comes to replacing neurons of a low level of functional activity, it may turn out that some minimum of genetic information is enough for their successful replacement of the crashed neurons. (And so, there are already appeared reports of partial successes in the treatment of Parkinson's disease - they are talking about low-level almost unconscious functions).

With Alzheimer's disease, such treatment (based on neurogenesis and partial regeneration of epigenetic information) does not work. AD affects the higher-level nervous activity of a person. There is no way to cope with such duties without epigenetic information.

However, a limited solution can also be useful - a limited amount of epigenetic information relating to a limited range of the patient's daily activities can be developed in the newborn neurons. All recommendations of the American Academy of Neurology, published recently (May 25, 2022) in the online edition of the journal Neurology, [13], and many

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other recommendations (usually accounting from three recommendations to 40 recommendations [14]) are based on utilizing these limited epigenetic capabilities. All of them are reduced to regular (repeated for better memorization and consolidation) actions of limited complexity - regular pedestrian passages, social communication and interaction, and cognitive exercises (reading, crossword puzzles). This is not a cure, all this is an attempt to slow down the death of neurons by creating their surrogate partial replacements. It can slow down the development of AD. But this is not a way to cure or alleviate Alzheimer's disease.

Possible ways to treat Alzheimer's disease (by genetic engineering of that part of a spoiled neuron, which is responsible for the processing and disposal of "information garbage"), which I hope that I have explained to the reader in this article.

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