Alzheimer's and Consciousness: How Much Subjectivity Is Objective?

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ABSTRACT: Does Alzheimer Disease show a decline in cognitive functions that relate to the awareness of external reality? In this paper, we will propose a perspective that patients with increasing symptoms of AD show a change in the awareness of subjective versus objective representative axis of reality thus consequently move to a more internal like perception of reality. This paradigm shift suggests that new insights into the dynamicity of the conscious representation of reality in the AD brain may give us new clues to the very early signs of memory and self-awareness impairment that originates from, in our view the microtubules.

Dialog between Adso and William, in Umberto Eco's The Name of the Rose, Third Day: Vespers.

"But how does it happen," I said with admiration, "that you were able to solve the mystery of the library looking at it from the outside, and you were unable to solve it when you were inside?" "Thus, God knows the world, because He conceived it in His mind, as if it was from the outside, before it was created, and we do not know its rule, because we live inside it, having found it already made."

KEYWORDS: Alzheimer disease, microtubules, consciousness, subjectivity, objectivity, dynamicity, self-awareness

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Introduction

Alzheimer's disease is a progressive neurodegenerative condition leading to the deterioration of the brain's memory capability and in late stages, we may observe changes in the consciousness concerning the external *versus* the internal notion of reality in which self-awareness is compromised.[1]

This compromised self-awareness is, in our view, corresponding to the presence of microtubular impairment by Tau fibrillization. The overall presence of Tau fibrils that impair synaptic and microtubular processes are fundamental to the progression of the disease[2] and probably to the deterioration of the SELF.[3]

In a ground-breaking paper with the lengthy title "Orchestrated Objective Reduction of Quantum Coherence in Brain Microtubules: The 'Orch OR' Model for Consciousness" by Hameroff and Penrose[4] the brain is described as a quantum computer whose main architecture are cytoskeletal microtubules, structures within each of the brain's neurons. Hamerhoff and Penrose[4,5] proposed in the mid-1990s that consciousness depends on biologically "orchestrated" coherent quantum processes in collections of microtubules within brain neurons, that these quantum processes correlate with, and regulate, neuronal synaptic and membrane activity of brain neurons (for more on the Orch hypothesis of consciousness see review). After the inception of the Orch hypothesis, numerous rebuttals have been presented.[4,6,7-12] A number of critics of the Orch hypothesis have been addressed by Hameroff and Penrose.[8,9] The debate has been opened from new data reported by Li et al[7]; Smith et al,[12] correction, Li et al[7] Smith et al[12] that Xenon 131 has 9 stable isotopes, but not all have the same anesthetic properties. Xenon is an elemental anesthetic. Still, the authors have evaluated isotopes with and without nuclear spin. They found that isotopes with nuclear spin are less potent, suggesting that the nuclear spin as a quantum property may implicate quantum mechanisms of consciousness.[11-13]

A neuron is interwoven with a cytoarchitecture comprised of microtubules that are utilized for a number of roles, from regulating the axon and dendritic forms or scaffolds,[13] transport of vesicles, to transport of proteins important for synaptic formation maintenance and transmission.[14]

To upraise the complexity of MT involvement in AD, 2 crucial papers (with references therein) have posted results concerning posttranslational modifications of tubulin[15] and the second, that microtubular impairment is independent of Tau filament formation in AD.[16] These results show that overall MT destabilization and cytoskeletal abnormalities, in a functional sense may affect the cognitive processes in the AD brain more by changes in the number of MT than by structural changes in the MT, that is a reduction of MT in pyramidal neurons that do not coincide with Tau fibrillization correspond

to AD genesis.[16] In our view, these MT "number changes" are a quantum mechanism that may coincide to also changes in the dynamicity of the conscious representation of reality in a brain affected by AD.

Results presented by Cash et al[16] and Zhang et al[15] show a presence of a compensatory mechanism or mechanisms as various posttranslational modifications of tubulin such as polyglutamylation, tyrosination, acetylation of alpha-tubulin (microtubules are composed of tubulin heterodimers made of alpha and beta-tubulin) have been found to change tubulin distribution in AD versus age-matched controls. These salvage mechanisms of tubulin post modifications in our view represent a survival mechanism of the brain as a whole, keeping the processes related to cognition to endure as long as they can. These results concur with our view that the internalization process of the affected brain by AD slowly deteriorates with time. We know that we are "in here" and that the world "is out there." In AD this dynamic internalization-externalization axis is altered.

The promoting ability for MT to apprise consciousness is based on their characteristics to be suitable for quantum effects, which includes its hollow inner core, crystal-like lattice, cell organization properties, and information processing. Microtubules are also reported to transmit photons in the UV range.[17] The quantum coherent effect has been reported in plant photosynthesis, bird brain navigation, sense of smell,[18-24] and recently in MT.[25-28]

Warm quantum vibrations in MT have been found in brain neurons.[29] Craddock et al[30] suggested that ions use the cytoskeleton network, in which ions flow along and through MT acting as transmission lines propagating cell signaling. Then Igamberdiev and Shklovskiy-Kordi[31] suggest that the problem of perception is resolved in the frame of what they call endophysics, a concept that shows that the objective, external world, can only be understood from inside of the "internal observer." Also, the authors state that observed objects cannot be distinguished from the internal quantum measurement process that is used to identify them.[32] Microtubule nanotubes are found in every living eukaryotic cell; these are formed by reversible polymerization of the tubulin protein, and their hollow fibers are filled with uniquely arranged water molecules. Thus, a monomolecular water channel residing inside the protein-cylinder displays a control property of optical and electronic features of the MT,[33] suggesting also that MT has quantum properties.

EEG rhythms may derive from deeper levels of brain organization, from the level of microtubular vibrations. Microtubule quantum vibrations (eg, in megahertz) appear to interfere and produce much slower EEG "beat frequencies."[32] In a clinical trial setting, transcranial ultrasound, aims at MT to resonate in the megahertz range stimulating the brain which resulted in improvements of mood in AD and brain injury.[32]

Results from Bilotta F et al,[34] showed that anesthesia selectively erases consciousness while sparing nonconscious brain activities via microtubules. Anesthesia is also known to induce AD type changes in susceptible individuals and experimental animals[34-36] and to be cognitively detrimental to AD patients.[34]

We introduce a view that micro-tubular impairment may coincide, or reflect to reduced externalization of the objective world, thus internalizing some of the conscious processes in the AD patient. This may objectify new determinants of reduced cognition and awareness that may be pre-accompanied by reduced memory in MCI and AD patients.

The concept of internalization of the "world" in an AD brain will be elucidated more by reviewing the work of Maturana and Varela and by the historical example of the patient zero Auguste D and her conversation with (Figure 1) Alois Alzheimer.[37]

The internalization versus externalization axis in AD: A new paradigm for research

***The dialog of dr Alois Alzheimer and patient zero, Auguste Deter*:** Auguste Deter, wife of a railway worker, born on May 16, 1850, a reformist by religious conviction, admitted to hospital on November 25, 1901. Assistant Prof. Nitsche, reviewed Auguste Deter's (AD) case in January and informed Prof. Alojz Alzheimer (AA) that the patient has unusual clinical symptoms.

Alzheimer's patient did an interview the next day as noted on the first page he wrote himself, carrying his conversation with the patient:

- What's your name? - Was his question (AA)
- Augusta (AD)
- And your surname? (AA)
- Augusta (AD)
- The name of your husband? (AA)

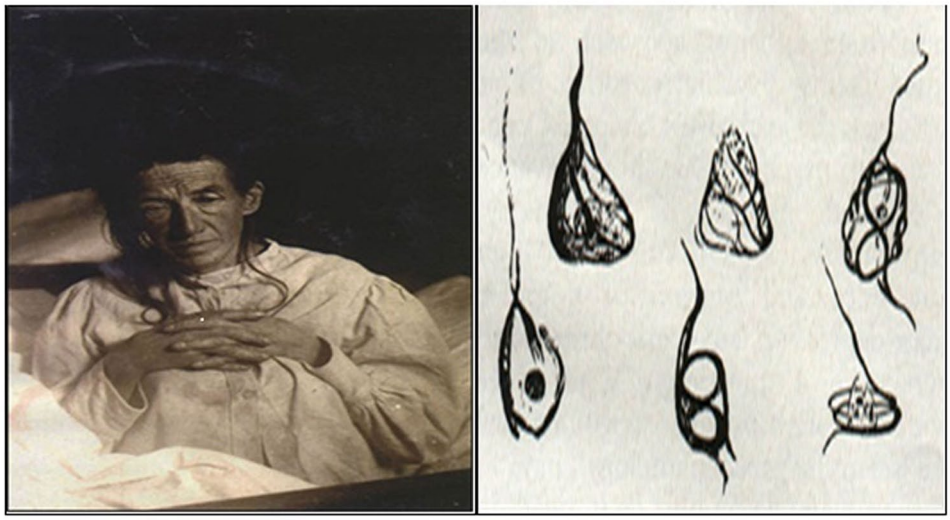
Augusta, I (AD)

- I'm asking the name of your husband (AA)
- For my husband? (AD)
- Are you married? (AA)
- About Augusta (AD)
- How long are you here? (AA)
- 3 weeks

- **Note:** Clearly the conversation shows that there is an impairment of self awareness and cognitive processes. She also shows the development of anosognosia.

Here's another example of the conversation between Alzheimer's and Augusta while she ate cauliflower with pork meat.

- What do you eat? - Alzheimer asked (AA)
- Spinach (AD)



Figures were taken from the book" 100 years of Alzheimer's Disease'' [Perry, G. *et al*, 2006]

Figure 1. Auguste D, the first patient of Alois Alzheimer and original drawings of Tau fibrils. Figures were taken from the book "100 years of Alzheimer's disease."

- She chewed but did not eat any meat, and then she said: - First I'm going to eat potatoes and then radishes (AD)

- **Note:** We clearly see that the internalization process has taken over objective realism.

Dr. Alzheimer showed her different objects and after a brief pause, she could not recollect what she saw. Meanwhile she spoke constantly and continuously repeated

- Mister Twin, I know Mr. Twin, twins (AD)
- Write Mrs d (eter) here, insisted Dr. Alzheimer (AA)

She wrote: Mrs but no surname. She could write her name if it is dictated but instead she wrote Augusa instead of Augusta. The patient had a difficult time to write sentences and phrases that have been requested from her, and had symptoms of compulsive verbal rehearsal. When she read she skipped orders and repeated the same sentence several times. She didn't look like somebody that understands what she has read. Her general physical examination was normal.

Augusta D experienced change of memory, language, thoughts, and ultimately behavior.

Later she was often upset and shouted. She often had panic attacks, named and repeated without cessation:

- I don't want them to hurt me, I don't want to hurt myself.. . .From that day her behavior had become hostile, often named and attacked anyone who wanted to examine her. She was always was under sedatives that were effective only occasionally. She was without any focus with the people who stayed in the common room, and hit people all the time. Could not understand why she had to be isolated from other patients. When they tried to talk to her she replied- I don't want to, no time. Symptoms got worse by the month.[37]

From the first interview we can see a time dependent deterioration of the I, or self-awareness of Augusta D. Here in this work Augusta D represents a matrix of changes in consciousness regarding memory and self-awareness in the neurodegenerative processes occurring in AD. AD shows a relative pattern of loss of memory and self-awareness that is repeated in dementia patients.

From the conversation above, except that we can see the loss of episodic and spatial memory, we also see a lack of self-awareness and a decrease of cognitive functioning in the course of the disease. This lack of awareness in affected subjects that are deficient in their own cognitive functioning we call anosognosia. Anosognosia is quite common in patients suffering from Alzheimer's disease, affecting from 20% to 80% of diagnosed individuals.[38-44]

Anosognosia is related to the earliest signs of AD.[38] In concert with anosognosia, the traditionally recognized characteristic of AD are episodic memory deficits,[45] but in the context of more subtle perception, language, and executive deficits are also present in AD. These findings may state that all these changes in self-awareness may be permeated by the alteration of *the internal versus external axis* that we propose as an early sign of AD.

On the other hand, AD might give us insights into how this axis is altered, and also represent a model of a dynamic property of consciousness of how we perceive, and experience reality.

It seems that the crucial phenomenon which defies consciousness and the specific part of it "the self" is the state of knowing. We know what is out there and we know that we are in here. This state of knowing is expressed in language.[46]

Linguistic changes have been for some time an area of research and have been an indicator of cognitive deterioration.[47-51] Also, artistic performance in painters has been a matter of study.[47,52-54] Later, a method of fractal embedded patterns has been found to be differentially expressed in affected painters *versus* individuals with a normal aging process.[55]

In both situations, we may observe how cognitive decline in AD patients reduces objective realism to an internal more subjective view that may be correlated with the severity of the disease. To better understand this shift, we have briefly reviewed the work of Maturana and Varela.[55]

In our view, humans are the only species that are seen to develop consciousness seen as an acquisition and instrumentalization of the internalization versus externalization processes that genuinely expand the human self on a broader and broader part of our immediate surroundings. This view will explicitly be resolved by the ideas first given from Varela and Maturana.[56,57]

Objectivity and the internalization versus externalization paradigm of awareness

There is a paradigm in scientific thought that the observer which wants to study a system is expected to expose a hypothesis of how the system functions and then to test it in order to make the best map of the territory that he is investigating. So, it is traditionally noted that the observer must stand on a point of objectivity in order not to influence the description he/she is observing. This access insists that they who are making the maps free themselves from their own maps in order not to be restrained by the self-reference paradigm.

There has been a number of investigators that challenge the notion that there is a world outside of us and that its properties can be accurately described, a territory that we can convey on a map.[58-68]

We do not want to challenge the notion of objective reality per se or as it is represented in the philosophy of representialism *versus* subjectivism as in solipsism, but to explore the notion of awareness as a dynamical self-reference system[69] that enables the paradigm of externalization of consciousness in humans. We can discern 2 components of consciousness, 1 is wakefulness which is abundantly presented by the latest neurosurgical research[70,71] and the second feature of consciousness is its contents, which is awareness.

Conscious subjects have phenomenal experiences or awareness of the internal and external world.

In our view, in AD the conscious awareness of the internalization-externalization axis is altered.

When Letvin et al,[70] published their seminal paper "of what the frogs eye says to the frogs brain" they haven't for 1 moment brought into question the existence of an objective reality that is independent from that frog.

The paradigm of objectivity is so profound that I wish here to describe the experiment at hand: "Using surgical techniques they rotated the eyes of Salamanders and frogs. In one of the experiments they rotated the eye of a tadpole. Once it matured into a frog they covered the operated eye and watched the frogs reaction to flies (food). The frog with minute precision throws its tongue toward its prey, the fly. But, when the normal eye was covered and when they opened the operated, rotated eye, an unusual thing would happen; the frog would throw its tongue in 180° angle, in the wrong direction, leaving him without a meal. By this experiment we can conclude that for the frog there is no down or up, or forward or backward outside from her."

From this experiment the authors concluded that an "objective" reality is not something outside per se.

The aerial of visual perception has enabled Maturana and Varela[72-77] to bring into question the understanding of perception as a simple operation that is limited to sending messages over telephone lines and "arriving" to the brain. This notion is also determined by our anatomy, that is lateral genicular nuclei is a switch master of the cortex prima which gets at least 5 nerve bundles from different parts of the cortex for every fiber from the retina that includes also feedback fibers from the visual cortex.[77,78]

This means that the lateral genicular nuclei is not only dependent from the activity of the retina but also from the intertwined connections that come from different parts of the brain.

If we relate these processes of the retina to our perception of color, the same paradigm arises as in the inverted eye of the tadpole, that there is not only 1 correlation between the wavelength of light and colors and seeing, but also how the brain in itself perceives and interprets light stimuli and building on these ground a whole picture of what is "out there." When we are seeing, the picture is composed and presented to our consciousness.[79] But there is a problem. If we reject the idea that the nervous system gathers information from the environment in order to make a representation of reality, then how can we avoid the trap of solipsism where the only reality is the internal one?

Again, from the Frog experiment Maturana and others have begun to question this assumption.[65,66,74,80-89] They could not test the activity of the retina and physical stimulus outside the organism, thus understanding that their subject reacts to colors that are not related to wavelengths of light that were coming from the object. So, we have to make a distinction of our experience of color *versus* the linear construct that the phenomenology of physical electromagnetic waves that induce perception by activating different receptors in the eye. Differentially said, seeing colors is a global phenomenon and not a local one.[79,85,87,89,90] This makes a problem for scientists that wish to "objectively" determine relationships between a stimulus and a sensation, as it is not possible to register a global activity of the retina, but only a reaction of individual neurons or fiber bundles toward an external stimulus.

Maturana and Varela[74,81-89,90] gave a pragmatic view of this dilemma. They state that perception cannot exist without interaction between the organism and observable electromagnetic waves. To differentiate colors, this cannot happen without a section between the emitter and the receiver, that is, the perception of color does not lie per se in the wavelength of light. So in the vision of a subject, it is not important how light affects the nervous system but also how the nervous system reacts to this stimulus. Interestingly, vision is affected in AD patients.[91]

Using a model of AD mice, AβPPswe/PS1dE9, Leinonen et al[92] have found subtle changes in the visual processing system in the retinas. Other changes have been reported, from nerve optic degeneration, retinal ganglion cell degeneration with a finding of retinal amyloid plaques to impairment in the visual tests,[93] visual evoked potential, and declined electroretinography.[94]

Results show that the retina reflects neurodegeneration processes in the brain,[95,96] thus altering the subject's perception, that is the internalization versus externalization axis that consequently affects awareness. The subject does not have to be conscious of these alternations, thus we may call it perceptual anosognosia.

The occurrence of the observer

Varela and Maturana[97-100] gave a notion to the importance of the observer: "*The observer describes things by making distinctions, but all these descriptions are self-referent or reflective : the created distinctions reveal us that : contrary to the usual view, a description when it is closely examined, reveals an observer.*"

We the observers distinguish ourselves just by making distinctions from what we are obviously not, the world.

The problem of self-reference comes from "language."[92] The paradox exists where the language engages with itself. The difficulty of a self-reference system is due to the impossibility to discern between the actor and the act.

By the act of observation, we remove 1 entity, or in the language of Maturana and Varele, a monad from its surroundings and conclude that they are 2 different things. When we make this distinction (to me it is more a differentiation, the discursive mind) we introduce the domain of coordinated actions, we make descriptions of descriptions. The observer is that fundamental entity that determines what is separated in the distinction. For the observer and what he describes are present in the language in which the distinction is performs.[90-93] Language is not conceived by a person to touch the outside world but that we are in language, placed in linguistic structural connections in which we make and improve ourselves.

Only a subject that can perceive, be aware, can report of what is happening in a given point and also state that this experience through language may inform others, that is "*the subject can objectify*" what he sees, it externalizes its subjective perception. In our view, not only the notion of colors but also the awareness per se is intertwined in "objectivity" by the notion of language. This awareness, this self-reference system is altered in AD as we have previously referenced.[47,48,49,101] This notion can also be concluded from the Augusta report. We hypothesize that "the internalization process" is activated very early in the disease and this process is later reflected in cognitive states as seen in anosognosia and brain hypometabolism anosognosia.[39-43,100]

Even though we cannot perceive reality as an objective truth as we always make our personal version of reality and even though we cannot resolve ourselves from the situation that we are describing, we still can objectify our subjectivity through self-awareness or as said beforehand that the "observer" is a fundamental property of consciousness in all of us, to discern what is outside of us or what is in us. In our view, this "internalization-externalization axis" is altered in AD.

Now, recent history and philosophy of science often suggest that this apparent objectivity cannot be characterized as dealing with things-out-there, as independent of mental contents-in-here.

What we take to be objective is what can be turned from individual accounts into a body of regulated knowledge. This body of knowledge is inescapably in part subjective, since it depends on individual observation and experience, and partly objective, since it is constrained and regulated by the empirical, natural phenomena. This brief reminder that the subjective is already implicit in the objective!

The paper addresses a new idea concerning how the dynamic representation of subjectivity versus objectivity has been affected in an AD brain, given the name "the internalization versus externalization process" of consciousness. Given the importance of this idea, we will try to address this issue. There are 3 main topics represented in this paper, MT in AD, objectivity, and awareness, and awareness and AD. The common denominator is the quantum reality paradigm in which the brain works.[22,23] In our view how a quantum brain utilizes consciousness is related to a dynamic aspect to how our perception is actively emerged in objectifying reality.[22] The observed objects cannot be discerned from the internal quantum measurement process that is used to identify them.[23]

Regarding how these processes can be utilized in a perspective to address pre AD stages, recently new research in the validation of subjective measure by using Awareness of self and Disease assessment (ASDA) was explored.[102] The authors measured awareness by evaluating different modes of the perception of AD subjects, from the environment, emotions, past and future, confrontation with difficulties, to how the AD subjects express their awareness of the disease itself, like denial, attribution, judgment, etc. The results suggest that awareness can be assessed through subjective experiences.[103] In a clinical sense awareness of the internal versus external axis can be evaluated by an ASDA modified questioner and it can also be

addressed through the Free Energy Principle (FPE) and predictive programming.[103-106] In a theoretical sense, a normal view of an internal versus external axis is in essence a homeostatic, balance mechanism. So, in Karl Friston and Mark Solms terms, if consciousness arises through a homeostatic mechanism, then according to Friston K et al, (2012)[10] the answer is free energy minimization. In a paper Moran KJ et al,[107] showed that in an aging brain the sensory data influences neuronal architecture to ensure its predictive power of the world through FPE minimalization.

These new ways to understand how the brain works in relation to the perception of the internal versus external axis by using FPE and Bayesian inference,[104-107] is in our view how these principles could be translated into direct (like fMRI) or indirect (ASDA) ways to diagnose early AD.

Perspectives

Self-awareness is a property of consciousness that enables us to perceive our external reality, that is that internal awareness helps us to get us out of ourselves. . . as we are more conscious of ourselves the more we are conscious of our environment. To be more consciously aware of our selves new research has opened possibilities from the use of yoga, meditation,[108-112] and techniques of mindfulness[113-117] that show that we can use our awareness to slow down the progression of dementia.[108-120]

A recent paper by Khalsa and Perry,[121] proposed the notion that changing one's lifestyle and attitude can make a difference in the outcome of AD. Managing chronic stress by yoga/meditation is considered a third pillar on what prevention stands. The other 3 pillars are diet and supplements, physical and mental exercise, and psychological well-being.[121]

Understanding more about awareness is an important element in envisioning new methods of early diagnostics AD and MCI. Presenting a correlation between language and artistic skills to the deterioration of awareness in AD puts us at the notion that impairment of awareness or changes in the internalization-externalization axis is a possible new sign of dementia that may correspond to memory impairment. Also, in our view changes in awareness of AD patients are at least in some part microtubule-dependent suggesting that consciousness is a quantum state of the brain in a quantum reality that integrates diverse properties of perception into a coherent experience.[121]

Author Contributions

All authors contributed to and approved this version of the manuscript. Conception, idea, and the new hypothesis: Bajic Vladan and writing, analysis, and drafting the manuscript: Perry George, Stankovic Ivana, Misic Natasa, and Zaric Bozidarka.

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