Alzheimer's Disease: Are Certain Parts of Memory More Affected by Alzheimer's Disease Than Others?

Winner, Science

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Alzheimer's Disease (AD) is a form of dementia that affects a person's cognitive ability. It is characterized by the rapid decline of cognition. The first case of AD was reported in 1907 but, even 100 years later, very little is known about the cause of the disease. The reason for our lack of understanding of AD is because there are no signature symptoms that only apply to AD compared to other forms of dementia. Therefore the diagnosis of AD is subjective; the only way to test for AD is through postmortem analysis of the brain.[1]

Primarily, synapses are most affected by AD. The synapses create the connections between neuronal cells in the brain. The synapses are critical when it comes to the performance of memory, cognition and a person's ability to perform tasks. They are the threads of our thoughts: without synapses we would not be able to learn new knowledge or access previous knowledge.[2]

With this in mind it is important to recognize the process of neuron proliferation. Neuron proliferation is the only time neurons can produce and multiply, and occurs during the embryonic period of development. After the embryonic period of development no new neurons can be produced.[3]

Due to advances in the postmortem dissection of the brain, we know there are two things that cause the neurons in the brain to die, resulting in cognitive impairment. Amyloid plaques and neurofibrillary tangles are irregular structures that form in the brain, and their cause is unknown. Amyloids are pieces of protein that are present in a healthy brain, but in AD the amyloid protein divides abnormally producing beta amyloid, which is toxic for neurons. This causes a build up of amyloid plaques and cell death.[4] The neurofibillary fibers are found within the cell of the neuron and cause the protein responsible for the cell's structure to twist around the cell's microtubules, like weeds wrapping around the supports of a house. The microtubules not only help with the structure of the cell, but contribute to the transportation of nutrients within the cell. When the cell has neuofibillary fibers twisted around the microtubules, the cell structure collapses, causing the neuron to die—the house collapses into rubble.[5]

In a healthy brain, presynaptic neurons suck up the dead neurons. Then, the glial cells, or supportive cells, eat any remaining dead cells. Without this function, neurotransmitters would not be eaten or uptaken, and the brain would not work. The electrical charges between neurons would be caught on the dead cells and not be able to get anywhere, almost like a traffic jam. If these cells cannot get anywhere,

they cause more neurons to get stuck, causing a backup of neurons and the disruption of nutrient transport, resulting in cell death. In AD, the amyloid plaques and the neurofibrillary tangles are unable to be uptaken or eaten up by the presynaptic neurons and glial cells, which causes more neurons to die.[6] This also explains why experts are unable to detect AD using PET or FMRI scans until the final stages of progression. It is not until the death of neurons is so high that the images of the brain show large dark spots where the neurons have died. The prognosis of AD is a general life expectancy of four to eight years, but can extend up to 20 years. The reason for the range in life expectancy is due to the fact that there are no symptoms of early AD and it cannot be diagnosed officially until autopsy.[7]

Purpose

Cognitive impairment increases as the disease progresses. In the early stages, patients forget simple operations, manifesting as a loss of words, tip of the tongue phenomenon, misplacing objects and minor confusion and disorientation. As AD progresses, patients have trouble manipulating everyday objects, fail to recognize familiar surroundings, and begin to lose track of people, places, important dates, and times which seemed universal to them only a short time ago. Patients report blurred flashbulbs of memory where they remember just what it is they are so desperately looking for.[8] This enables them to recognized the rapid decline and loss of their cognitive abilities. This causes patients to express aggression and depression, which to family members is completely out of character. AD causes a loss of self and independence among patients. In this review, I hope to embellish the symptoms of AD, more specifically related to brain function. Are certain parts of the brain's memory system more or less affected by AD than others? Is there anything we can do to help patients with AD retain a shred of their sense of self?

Methods for Studying Alzheimer's Disease

Transgenic APP/PS1 Mice

In order to be able to study AD the brain must be dissected after death. There is very little evidence on the causes of AD in humans due to ethical constraints on research. Therefore, the majority of research experiments done on AD are on model species. Even having the ability to give animals simulated forms of AD, we still have limited information regarding the treatment of AD.

In the mouse model researchers state "hippocampus long term potentiation (LTP) is a form of synaptic plasticity accepted as a biological model of learning and memory that has emerged as a cellular model for studying mechanisms involved in cognitive deficits related to AD."[9] With this in mind, researchers want to know if learning and memory will improve in mutated human amyloid precursor protein(APP/PS1) mice, a model of human AD, with constant treadmill activity by enhancing their LTP. The study consisted of four groups: wild-type controlled, wild-type with exercise, transgenic mice controlled and transgenic mice with exercise. The mice were required to run treadmills and complete

water maze tests for five months. At the end of the study six mice from each group were sacrificed in order to analyze the brain.

The APP/PS1 mice showed that the treadmill and water maze did not affect mouse awareness or vision. During the treadmill exercise APP/PS1 mice were found to have fewer learning ability deficits. The wild-type mice, which were given exercise, showed greater ability to complete the maze. The water maze decreased the learning deficits placed on the APP/PS1 mice as well as enhanced the performance of the controlled wild mice. "Regular moderate physical exercise can improve cognitive function, and exercise is known to influence risk and development of AD throughout the life time."[10] This suggests that regular exercise may decrease the mouse model's chances of getting AD. It would also be beneficial to study healthy elderly who have led active lives compared to elderly patients who have led less active lives over a period of years to see if the less active are more likely to get AD.

APP/PS1 Transgenic Mice Administered with Melatonin

Melatonin was originally prescribed to AD patients as a sleeping aid, in the form of an oral treatment. Research suggested that melatonin taken orally over a 2-3 year period helped deter the cognitive impairment of AD.[11] This probed researchers to test transgenic APP/PS1 mice to see if melatonin can actually be used as a treatment of AD, and if it actually stops the cognitive impairment and deterioration of the brain caused by AD. The study consisted of four groups: APP/PS1 mice, control and experimental, and normal mice, control and experimental. Experimental groups were given 0.5 mg of melatonin in their drinking water beginning at 2.5 months of age up to 7.5 months, when they were sacrificed so their the brain tissue could be analyzed.[12]

Results from the APP/PS1 mice who were given melatonin on a regular basis showed that melatonin prevented the deterioration of the brain caused by the transgenic APP/PS1 form of AD. Melatonin improved memory abilities and special referencing in the APP/PS1 mice, but did not impact the ability of non-transgenic mice to complete a testing maze.[13] In other words, melatonin had no effect on healthy mice, only transgenic APP/PS1 mice. Melatonin is able to pass through all the cells of the brain and not cause any harm, while reducing buildup of amyloids in the brain. Currently AD patents are prescribed melatonin as a sleep aid. More research is need in the effects of melatonin on humans with AD in order to help future patients with AD.

Manipulating Colour and Other Visual Influences Picture Naming: AD and Normal Controls on Humans

Researchers believe that there is evidence that images with specific colours have an effect on AD patients' ability to recognize familiar objects.[14] Researchers conducted an experiment with two groups: AD patients and normal control. Subjects were required to name-identify line drawings and photographs. In the first part of the study the participants were shown the black and white and coloured drawings, and asked if they could identify or recall seeing the item. Next they were shown the black and white and coloured photos, and then asked again if they could identify or recognize the items.

The results of this study showed that patients with AD were able to identify photos that were incorrectly coloured, but they were unable to identify the appropriate colour, or the item in the photograph. Researchers suggested the reason for this is because "semantic representations only specify functional and associative knowledge and visual features are coded in structural representations."[15] Researchers also noticed that patients were able to recognize errors more effectively for living things in comparison to non-living things. The structural representations used to identify the photographs and drawings are believed to come from the patients' long-term memory system.[16] This suggests that on some level, patient with AD are able to recall their long-term memories of familiar items that do not change in colour.

Autobiographical Memory Retrieval in Humans with AD

During the natural process of aging, personal autobiographical memories (AM) transfer from the episodic memory system, which is responsible for the encoding and retrieval of memory, to the semantic memory system, which is responsible for general fact-based knowledge. Characteristics of the shift in memory functions during the deterioration of the brain during AD are unknown.[17] Researchers speculate that "semantic retrieval might compensate for episodic retrieval failure. Thus it is not surprising that the episodic-to-semantic shift from AM becomes amplified with memory impairments."[18] The hippocampus enables memories to be retrieved with vivid detail, regardless of the recency of the memory. This implies that the hippocampus aids in the retrieval of episodic memory, as well as that AD degrades the episodic process of retrieving AM.[19]

In order to test this theory, researchers must test the AM retrieval of semantic memory. They decided to test semantic memory in two groups of patients: a control group of 22 healthy elderly patients, and 21 patients subjectively diagnosed with the early stage of AD. Subjects were given a controlled setting, where they were measured on their performance of matching semantic statements, and an experimental setting, where they were measured for their performance of AM statements based on previous personal interviews.[20]

Research showed that in both healthy elderly and AD patients AM was consistent and similar in length, but AD patients revealed a shift from their episodic memory to their semantic memory during the AM retrieval.[21] Results also showed that healthy elderly AM were more concentrated with episodic memory. This suggests that certain functions of the brain are affected differently than others for AD. Focusing attention on those specific functions may lead to earlier diagnosis and treatment of AD.

False Memory Effects in Humans with AD

The inability to find words is one of the most obvious signs of possible dementia in the elderly. If researchers can better understand what part of the memory system causes patients to misplace words, therapies for these systems may help patients retain at least a portion of their sense of self.[22] The semantic memory system is responsible for general knowledge and facts. This is why patients suffering

from AD have a hard time recalling names for familiar items. With regards to patients having the ability to distinguish between relevant and irrelevant information when trying to recall or identify objects, it is important to understand the tagging model of recall and recognition. This theory suggests that as you experience and come across items, they are tagged. Items tagged with similarities are known as targets, which accounts for errors due to similarities when it comes to recall and recognition. When patients with AD are asked to identify objects or recall words, they are unable to distinguish irrelevant or similar tags from the correct tags.

To test this theory, researchers gathered two groups: young adults, and patients with possible AD. They were given lists of words which had similar associations, such as cash, flow, dough, finances, capital, check, and salary, etc. They were first asked if they could recall any of the words, then if they recognized any of the words.

In the young adult group, the participants recalled the word not presented to them 40% of the time. The patients with possible AD were more likely to fall subject to false memory errors—faulty tag retrieval. Researchers assume "[activation spreads] through the semantic network to related words or concepts as list words are presented at study" (Waldie, et al., 282). If the words presented in the lists were not all from the same association such as money, there would not have been as high of a chance of recalling false memories. In future studies it might be beneficial to mix familiar words together such as drink, fluid, juice, cash, check, and salary to see if there would be different results. A possible confound in the study suggests that patients with AD might have not actually remembered the words but been able to associate them with the words given, or have been randomly guessing. Researchers conclude that "understanding the activation process in the semantic network may provide insights into the strategies that can be used to implicitly cue words or memories that seem unretrievable by persons with AD."[23]

Effect of Echoic Memory of AD patients: Music

Echoic memory is auditory information, which can be present even after the stimulus is gone. The echoic memory theory supports the idea that most of the information that makes it to the long-term memory system is verbal. This also raises the question whether AD patients experience differences in the decay of their echoic memory in relation to other memory systems. To test this theory within a single case study, an 82-year-old musician with possible AD was studied for a period of seven years. The researchers hoped to distinguish whether or not patients with AD are able to recall or recognize music from their past. Researchers asked the man to play previously learned piano compositions and asked him to identify the titles of music and the composer. The course of this study tested the man's retrograde procedural memory through the impairment of his declarative memory, of both semantic and episodic memory systems.[24]

During the later stages of AD, the researcher brought the man to the piano to see if he could play anything. He could not remember compositions, but when the researcher started the songs, the man

was able to continue playing the songs. He managed to complete 13 correct attempts playing familiar music. He was unable to identify the composer or title of what he was playing.[25] Researchers concluded that "the dissociation occurs for both retrograde and anterograde memory, by poor scores in testing free recall, cued recall and recognition of new information" (Crystal et al., 1416). The ability of the musician to continue playing music, once cued, suggests that his procedural memory was intact. Researchers hypothesize that the deterioration of procedural memory in patients with AD is something that occurs during the final stages of the disease. With more understanding of recall and recognition of music in patents with AD, we might be able to help patients retain more of their sense of self.

Discussion

There is a lot of research suggesting that activity helps deter the possibility of being diagnosed with AD, but further research is needed on brain plasticity of APP/PS1 mice. Most mouse model studies show conflicting results, as well results which vary from transgenic forms of AD to human forms of AD. There is more support that APP/PS1 transgenic mice administered with melatonin have less brain degeneration caused by transgenic AD. More research is needed on human participants before the study can be conclusive. Mice and rats have also shown conflicting results when orally consuming melatonin, suggesting the need for more research.

The manipulation of colour and other visual influences in picture naming activities suggested that patients with AD had severe impairments in their semantic memory, but were able to use part of their structural memory to assist them with the task. This study is very interesting but needs more research. It would be interesting to see if smells and texture had an influence on patients with AD.

The false memory effects in autobiographical memory retrieval in humans with AD suggests that certain functions of the brain are affected differently than others for AD. In the mild cognitive impairment of normal ageing vs. memory deterioration study, AD patients were more likely to fall subject to false memory errors. It is important that we continue to study the effects of semantic and episodic memory so that maybe some day we will be able to produce an earlier diagnosis and treatment of AD.

In conclusion, despite multiple avenues of research there is no cure as of yet for AD, or any definitive symptoms prior to postmortem autopsy. More research is needed on AD in order to try and come up with more treatments for patients with AD, in hopes of giving them a better quality of life.

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[1] Mahar, Chris. 17 June 2011. Lecture.

[2] Mahar, Chris. 08 June 2011. Powerpoint.

[3] Mahar, Chris. 08 June 2011. Powerpoint.

[4] Mahar, Chris. 08 June 2011. Lecture.

[5] Mahar, Chris. 14 June 2011. Garret Powerpoint.

[6] Mahar, Chris. 14 June 2011. Garret Powerpoint.

[7] Mahar, Chris. 08 June 2011. Lecture.

[8] Mahar, Chris. 17 June 2011. Lecture.

[9] Hui-li Liu, 308

[10] Hui-li Liu et al., 310

[11] Olscese et. al., pg 82

[12] Olscese et. al., pg 83

[13] Olcese et. al., pg 87

[14] Zannino et al., pg 2571

[15] Zannino et al., 2572

[16] Zannino et al, pg 2571

[17] Meulenbroek et. al., pg 331

[18] Meulenbroek et. al., pg 331

[19] Meulenbroek et. al., pg 332

[20] Meulenbroek et. al., pg 332

[21] Meulenbroek et. al., pg 334

[22] Waddie et. al., pg 281

[23] Waldie, et al., 294

[24] Crystal et. al., pg 1415

[25] Crystal et al., 1416

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