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From Amyloid Plaques to Behavioral Patterns: A Fundamental Synopsis of the History of Alzheimer's disease and The Amyloid Cascade Hypothesis

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I. INTRODUCTION

Dementia, a leading killer in the aging population of the United States, is a cognitive ailment most frequently born from Alzheimer's Disease, which itself is a neurodegenerative disease that is known to start with the buildup of amyloid-beta peptides, molecules that are associated with the buildup of plaques, and these are implicated in the onset of Alzheimer's disease (Dicks et al., 2019). The amyloid beta-peptide is created through a proteolytic process, the breaking down of proteins into smaller amino acids most often catalyzed by enzymes called proteases, involving a transmembrane protein called the amyloid precursor protein (Chen et al. 2017). Interestingly, although there is enough of a strong positive correlation between amyloid plaque buildup and Alzheimer's that it is widely considered a causal factor, the mechanisms by which amyloid plaque accumulation facilitates the onset of Alzheimer's remains unknown. It is this lack of knowledge that allows Alzheimer's to continue its deadly reign of terror, even in the face of ever-increasing scientific and medical technology.

According to a 2020 report from the Alzheimer's Association, more than 122,000 Americans died from the neurodegenerative disease in 2018, making it the sixth leading cause of death in the country. It is apparent that a better understanding of amyloid buildup and the role that it plays in exacerbating Alzheimer's will be critical to finding a more efficient treatment, or even possibly a mechanism that offers a cure. For this reason, the bulk of modern Alzheimer's research is centered around beta-amyloid plaques and the ways in which medicine may be able to prevent or reverse their accumulation over time.

The disease itself was discovered by Dr. Alois Alzheimer as he evaluated a patient in his care at an insane asylum in Frankfurt, Germany (Stelzmann et al., 1995). He kept a detailed account of her degeneration, until the patient's death a year later. Posthumously, Dr. Alzheimer used a technique referred to as silver staining histology, the use of silver to microscopically assess organic matter by selectively staining it to make certain elements stand out, and observed that there were a series of odd phenomena, not in keeping with our standard anatomical design. Among other things such as entangled neuronal fibers, Alzheimer wrote that he observed plaques, which, unbeknownst to him at the time, were composed of the amyloid-beta peptide. A medical handbook published in 1910, the *Handbook of Psychiatry*, by one of Dr. Alzheimers's mentors, Emil Kraepelin, recognized the disease for the first time and accredited its discovery to Dr. Alzheimer, and a year later diagnoses of the ailment were being made in Europe and America alike. Alzheimer had drawn a series of sketches of the anatomical distortions observed in his first patient's brain, and these were published in Kraepelin's medical handbook as well and became the standard by which the disease was diagnosed, post-death of course (Bondi, Edmonds, & Salmon, 2018).

Shortly thereafter, the first two editions of the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders* provided formal criteria by which the disease could be defined and diagnosed. From this point on, several niche researchers explored the field of dementia and Alzheimer's, most notably a study that showed that the degree of severity of an individual case of Alzheimer's was strongly correlated to how well the affected individual scored on a cognitive assessment, with worse cases scoring lower and more mild cases fairing far better (Blessed, Tomlinson, & Roth, 1968). But aside from this, little new knowledge was acquired for roughly seventy years after the disease's discovery, principally because the body of knowledge surrounding an issue of near-microscopic scale, can only progress as fast as the technology that is being used to assess it.

It would not be until a famous assertion by neurologist Robert Katzman, based on a summary of previously collected data, which led him to conclude that Alzheimer's was one of the primary causes of death in the elderly community, that significant credence was given to the disease and its study, both from a cognitive neuroscience and behavioral standpoint (Katzman, 1976).

By the mid-1980s, it was well understood that amnesia of various forms, described as a noteworthy decrease in episodic memory capability, is the earliest and most easily identifiable symptom of Alzheimer's (Bondi, Edmonds, & Salmon, 2018), hence the reason memory loss is seen as the hallmark condition of Alzheimer's disease to this day.

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The medial temporal lobe, which includes the hippocampus, a subcomponent of the brain which is heavily involved in most aspects of memory recall and learning (Anand & Dhikav, 2012) is one of the primary areas affected by Alzheimer's disease early on, so memories that are not as deeply encoded are more susceptible to being lost temporarily or altogether, even at the earliest stages of amyloid plaque buildup in the hippocampus. It would be revealed in the mid-1990s that other areas of the brain are subjected to the same plaque buildup and neurodegeneration, subsequent to the hippocampus, and this would facilitate a loss in cognitive function and those behaviors that are principally emergent from affected neocortical areas as a consequence (Hodges & Patterson, 1995).

By the turn of the century, the implications of the disease were better understood enough so as to realize that episodic memory is not the only memory that is impaired by the disease. The spread of the neurodegeneration to other parts of the brain is generally thought of as branching out from the hippocampus, leading to a reduction not only in function but in memory that is likely stored in these areas. For that reason, it is now understood that Alzheimer's Disease, depending on the severity, will purge the long-term memories as well as the short, as gray matter atrophies more severely as the disease progresses.

Throughout the 2000s and early 2010s, a great deal of the biophysical processes and the anatomical distortions that are associated with Alzheimer's disease and its many variations that still hold true today were discovered. In truth, most of them are so minute in scale that it would not serve the purpose of this particular paper to explore them in any great detail, but they have accumulated sufficiently to formulate the neuroscientific community's best theory for the onset, progression, and culmination of Alzheimer's disease yet, a framework that offers a universal, and potentially causal explanation for Alzheimer's disease, predicated on the acceptance of the observed fact that amyloid buildup in various neocortical regions inhibits the functions in a manner that corresponds to the criteria given in the *Diagnostic and Statistical Manual of*

II. MENTAL DISORDERS

The theory was popularized and called the *Amyloid Cascade Hypothesis* (Jack et al., 2010), and has since been regarded as the most plausible theory for the onset of Alzheimer's disease both in early and late cases. There are two primary variants of Alzheimer's disease, one of which is referred to as familial Alzheimer's disease (FAD) and is characterized by dominant mutations to the aforementioned amyloid precursor protein that result in an over-accumulation of amyloid plaques in critical cerebral regions including the hippocampus and the entorhinal cortex and has also been attributed to mutations in the gene's called PSEN1 and PSEN2, which are thought to contribute to the overaccumulation amyloid plaque as well (Sherrington et al. 1996). This variation of Alzheimer's is inherited, as these genetic mutations are passed down from the parents, but this only accounts for 4-8% of all total Alzheimer's cases. With that said, the onset of familial Alzheimer's disease occurs much earlier than most cases, with many patients falling victim to the associated symptoms before they are sixty years old (Blennow et al., 2006). On the other hand, the bulk of Alzheimer's diagnoses are late-onset cases, commonly referred to as sporadic Alzheimer's disease, and this variation is thought to stem from a mutation to the amyloid precursor protein, but not from the mutated PSEN1 and PSEN2 genes (Cruts et al. 1995).

To date, this is the extent of the biological framework that is used to describe and diagnose Alzheimer's as well as in the development of drugs and treatments for the disease, all of which have thus far been ineffective. As mentioned earlier, a better understanding of amyloid and how it affects the effects our cognitive processes is critical for the combatants of the disease, but such knowledge is not yet available. One of the primary ways that neurologists are attempting to broaden the scope of our knowledge on Alzheimer's disease is the evaluation of the behavioral side effects that are emergent from the disease, and examining correlations between anatomical atrophy and behavior on a case by case basis to look for commonalities amongst people groups and variants.

Many of the behavioral implications of early and late-onset Alzheimer's are shared and it is widely theorized that changes in the behaviors of affected individuals are derivative of neurodegeneration that impairs the function of the neurotransmitters (Cummings & Kaufer., 1996). There is a body of work that suggests external stimuli may precipitate either mild or drastic alterations in behavior depending on the type and intensity of the stimulus in question, and these include things like bright lights, loud noises, and mild pain, as well as alterations to the setting of a room or the social situation (McCann et al., 2004).

Observations in a clinical setting have shown that behavioral alterations are not overly variable in terms of type or structure when speaking of different types of Alzheimer's (despite the fact that early-onset Alzheimer's is generally longer lasting and ends up being more severe in terms of degeneration) and that they share a common root in temporal sensitivity, with the term "sundowning" being popularized and descriptive of an evening peak in behavioral disturbances (Bliwise, 1994). The fact that research has shown that Alzheimer's patients of all types are, on average, sensitive to this transition from day to night, there is an increasing belief in the fact that this transition from day to night facilitates cognitive impairment as a result of hyperactive cerebral components associated with circadian rhythms that may have some effect on hormonal secretions and balances. Although the biological factors that may contribute to this effect have not been studied, there have been several studies that have used direct observation to examine the

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consistency and validity of this effect, most notably, the paper entitled "Temporal Patterns of Negative and Positive Behavior Among Nursing Home Residents With Alzheimer's Disease," authored by Judith McCann and her team.

Through the direct observation of 177 nursing home residents over the age of sixty-five who had been diagnosed with Alzheimer's disease, the team scored subjects on a discrete scale of occurrence or nonoccurrence of the target behavior, looking particularly for a deviation from what they perceive to be a normal mental state, over sixty intermittent bouts of observation only five minutes long. Once data was compiled for the participants after twelve consecutive days, which included the standard times of day in which the observers saw drastic changes in the behavior of the patients, the study found statistically significant variation in behavior, that, on average, peaked right before sunset (McCann et al., 2004). The study was able to effectively prove that behavioral changes in this sample of Alzheimers patients consistently varied at sundown, implicating that behavioral alterations as a result of compromised cognitive function in patients who have been diagnosed with Alzheimer's disease, still share commonalities from case to case, one of which is their temporal basis. Finding more of these commonalities will aid in determining what the roots of the issue itself are and will serve to bridge the gap in our scientific understanding that exists between amyloid plaque buildup and the onset of Alzheimer's disease. The causal factor lies somewhere in between these steps, and creating a cure may very well reside on whether or not we can determine what this causal factor is.

Another area of primary concern when it comes to the behavioral assessment of Alzheimer's disease is adherence, which is broadly defined as the extent to which an individual who is being treated for some type of psychological or physiological illness will comply with the treatments being designated to them. For example, the failure of a young child with Attention Deficit Hyperactivity Disorder (ADHD) to take the medications that he has been prescribed, would be considered poor adherence. In a larger sense, medications and treatments can be assigned adherence rates, which is simply the rate at which those prescribed them adhere to them. Daily exercise, for example, often has a lower rate of adherence than a pill of some sort, because people are less likely to stick to the prescription of physical activity, as they find it more difficult than just taking a pill. In the case of Alzheimer's disease, the cognitive impairment that is a consistent side effect and grows in severity as the disease progresses is a significant barrier to overcome for both the patient and the doctor when it comes to adherence. As a result, Alzheimer's disease in elderly patients is a significant predictor of low adherence to drugs that are prescribed to maximize health and mitigate pain to the fullest extent possible while they are living with the disease.

In an effort to combat low adherence in Alzheimer's patients a number of different methodologies have been tried, including the integration of the medication into the daily routine of the patient (Arlt et al., 2008). Because one of the most positive predictors of adherence in other areas of psychological health is social support and an aura of community, one of the most effective strategies for reducing accidental nonadherence is consciously increased communication between the patient and doctor, as well as more frequent follow up visits, and support group therapy (Brady & Weinman, 2013). The notion that social support may be an effective way to combat nonadherence is compounded by the fact that heightened rates of adherence have been shown in patients who have received a noteworthy level of support from family and friends (DiMatteo, 2004). But ultimately, the issue of adherence will become a much more significant one when there is an actual cure for the disease. Although steps can be taken now to improve the quality of the life that one lives while they have Alzheimer's, it is still an irreversible ailment that will generally end in death sooner rather than later. Once there is a cure, nonadherence will not only be deadly, it will be *unnecessarily* deadly. So, research is budding in the field of adherence in Alzheimer's patients, but it is still limited. That said, funding for such research is critically important for the life-saving capabilities that it will have in the future.

No treatment for Alzheimer's has had any effect at curing the disease or reversing the neurodegeneration process thus far. Virtually all proposed and tested treatments that have failed have been aimed at reducing amyloid levels in the brain, under the assumption that the amyloid cascade hypothesis outlined above is correct. But, if drugs with this specific aim continue to fail, neurologists around the globe may be better served to abandon the amyloid cascade hypothesis in favor of a reworked theory of generation and exacerbation of Alzheimer's disease. It is plausible that amyloid buildup is a consequence of an underlying causal process or system, rather than being the cause itself. Perhaps amyloid should be treated as an indicator of Alzheimer's disease and its severity, rather than as the causal agent. But, regardless of whether or not the amyloid cascade hypothesis is valid, research that involves the behavioral consequences of Alzheimer's needs to be funded and conducted more frequently and expansively, as devoid of new technology or miracle theory, the best bet for determining the causal factor(s) of Alzheimer's disease will be the direct observation of patients and the finding of consistencies between unrelated people groups who are infected in the disease. Universal symptoms may be indicative of universal biological manipulations to the brains of those affected, and being able to trace consistent behavior back to their anatomical origins may lead to the discovery of more effective treatment, or possibly even a cure.

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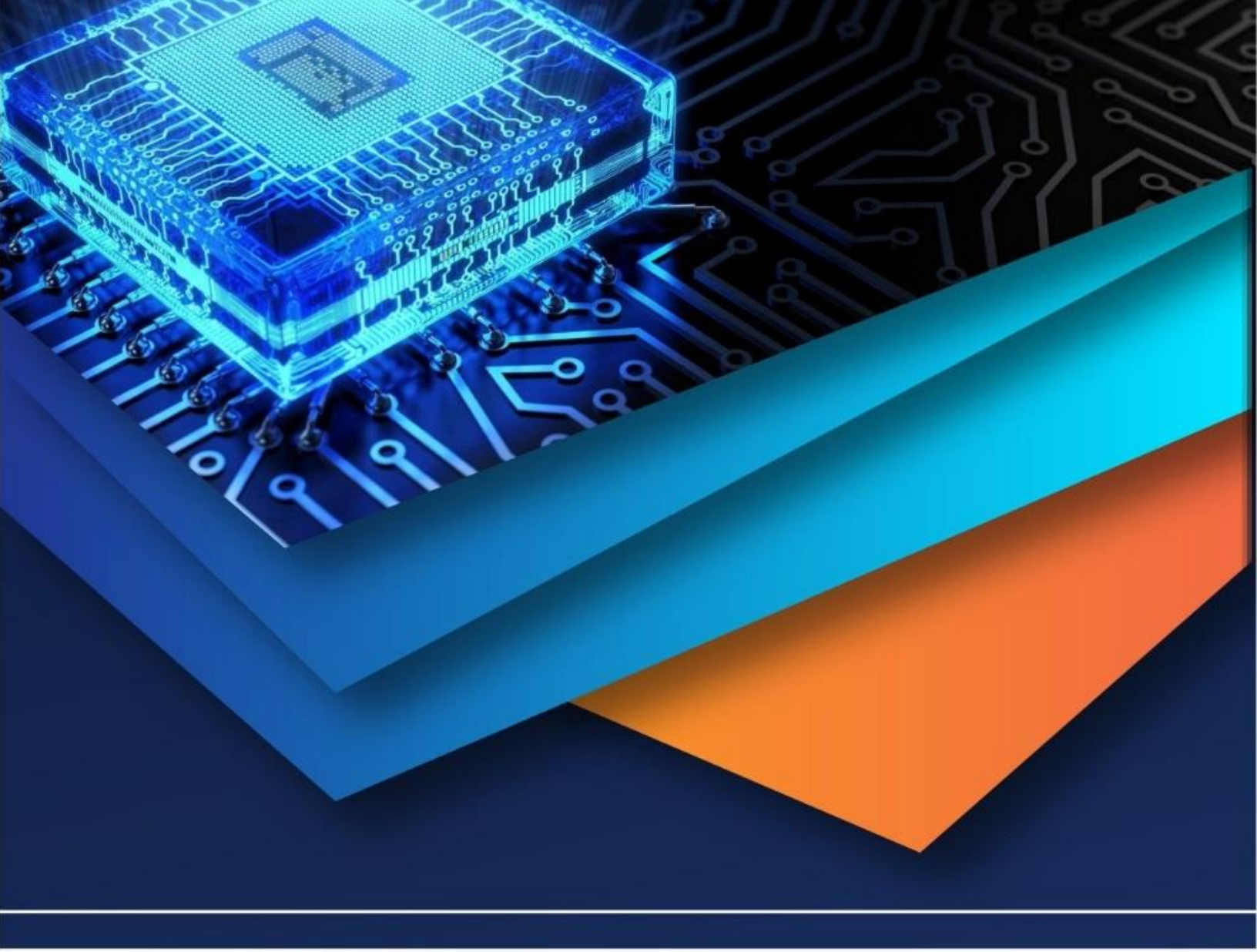

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