The current neuroscientific understanding of Alzheimer's Disease

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INTRODUCTION

Alzheimer's disease is a neurological illness resulting in the deterioration of brain regions that control memory and cognitive function. Not only is there no cure or effective treatment, but it is also degenerative, meaning that its severity only worsens over time. Through years of neuroscience research, scientists have discovered much of what happens in the brain during the onset of Alzheimer's disease and how this causes its symptoms, leading to various hypotheses including the potential roles of temporal lobe atrophy, neurofibrillary tangles, and amyloid plaques in its etiology and progression. Although Alzheimer's disease affects millions every day, many are unaware of how it impacts the human body physiologically, emotionally, and psychosocially. This overwhelming lack of general knowledge regarding the main characteristics, physiological causes, and diagnostic criteria of this illness makes it difficult to recognize the presence of Alzheimer's disease within oneself, friends, and family members, which could in turn stop patients from receiving necessary care and supervision. Therefore, knowledge of the relationship between neuroscience and Alzheimer's disease is essential for proper diagnosis and treatment. The following literature review explores research investigating the relationship between neuroscience and Alzheimer's disease and how this illness affects the body from many facets.

OVERVIEW

DEFINING CHARACTERISTICS AND DIAGNOSTIC CRITERIA

Various external symptoms must be present in order to classify cognitive decline as Alzheimer's disease. The need for diagnosis often goes unnoticed because not only will the patient's cognitive decline be attributed to old age, but their loved ones are also unaware of how signs of healthy aging differ from that of Alzheimer's disease (Alzheimer's Association, 2019). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, patients must exhibit numerous symptoms including both a decline in memory and one of the following cognitive defects: aphasia—loss of speech abilities, apraxia—loss of motor skills, agnosia—loss of sensory processing, and trouble with executive functioning (American Psychiatric Association, 2000, p. 157). As Alzheimer's disease progresses, these symptoms become more apparent, leading to diagnosis if handled properly, which requires bringing patients to a primary care physician who will obtain a medical and family history, conduct cognitive tests, and perform physical and neurological examinations. Sometimes, medical professionals will also order magnetic resonance imaging (MRI) scans to ensure that the patient's cognitive decline is due solely to atrophy rather than other causes such as a tumor or trauma (Farran *et al.*, 2011, p. 210). Doctors run multiple tests to confirm the diagnosis so that patients can be properly cared for, whether that means moving in with a family member, regularly visiting a neurologist, or relocating to a nursing

home. By increasing the general public's awareness of these symptoms, Alzheimer's disease patients will live a safer life of better quality.

SYMPTOM PROGRESSION

Since Alzheimer's disease is irreversible, symptoms only worsen with time; however, new symptoms can manifest depending on the stage and severity of the illness. According to Jost *et al.* (1996), "Psychiatric manifestations of depression occurred more than 2 years before diagnosis… Psychotic symptoms manifested around the time of diagnosis… whereas agitative symptoms occurred in the first year after diagnosis" (p. 1078). This explains how Alzheimer's disease typically begins with depression and psychotic symptoms but can later be characterized by aggression and irritability as it progresses. As the illness advances from early- to late-stage, these cognitive changes only become more apparent and warrant the need for professional care. Surprisingly, the progression of this illness occurs at a faster rate than expected due to such rapid brain deterioration; the temporal lobe of an Alzheimer's patient declines at a rate of 15.1% per year while that of a healthy person is only 1.5% (Jobst and Grossberg, 1994, p. 829). Not only are these symptoms severe, but they also must be recognized as early as possible since waiting for even a short period of time can significantly worsen the prognosis for an Alzheimer's disease patient.

LITERATURE REVIEW

Due to a lack of public awareness of general aspects of Alzheimer's disease since its symptoms are so similar to that of regular aging, numerous recent works discuss these components in order to share valuable information about the internal symptoms, progression, and external signs of Alzheimer's disease (Alzheimer's Association, 2012, p. 6). For instance, Thies and Bleiler (2011) describe the diagnostic criteria, warning signs, general prognosis, and typical characteristics of Alzheimer's disease while Jost and Grossberg (1996) chronicle psychiatric changes in Alzheimer's disease patients as the illness worsens from early- to late-stage. Furthermore, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (2000) details the criteria for an Alzheimer's disease diagnosis by a medical professional, informing readers of the overarching themes of Alzheimer's disease and what to screen for in potential patients.

There are many hypotheses surrounding the neuroscience behind Alzheimer's disease and its physiological causes. For example, Bancher *et al.* (1989) explore Alzheimer's disease etiology by discussing the potentially harmful neurological effects of neurofibrillary tangles in the brain, which lead to memory loss and neuronal cell damage. In comparing brain tissue in patients with Alzheimer's disease to that of control cases without dementia postmortem, they found numerous neurofibrillary tangles located in spaces typically occupied by

healthy neurons in Alzheimer's disease patients, supporting that significant cognitive decline in this illness correlates with the growth of these substances due to resulting neuronal damage. Alternatively, Killiany *et al.* (1993) investigates the contribution of temporal lobe atrophy to Alzheimer's disease development using magnetic resonance imaging (MRI) to compare the brains of Alzheimer's disease patients to that of healthy controls of the same age to determine which parts of the brain are compromised with disease progression. These researchers explore the same theory as Jobst *et al.* (1994), who detail the rate at which brain tissue changes in Alzheimer's disease and how the temporal lobe affected in particular. Studies surrounding the temporal lobe's role in Alzheimer's disease differs from that of neurofibrillary tangles because they are conducted antemortem, meaning that the researchers studied living patients to examine temporal lobes atrophy while neurofibrillary tangles were observed postmortem. Lastly, Hardy and Selkoe (2002) examine the potential for plaque aggregation in the brain to induce Alzheimer's disease by detailing this hypothesis' successes as well as shortcomings. Known as amyloid plaques, these detrimental substances are prominent Alzheimer's disease patients, leading researchers to believe that these aggregates might be an underlying cause of this illness. However, they also note that this theory is under criticism since the number of amyloid plaques in the brain does not correlate with Alzheimer's disease severity, leading scientists to think that amyloid plaques might contribute only to its onset rather than progression. Each of these works focus on different hypotheses that explain potential physiological causes of Alzheimer's disease and how this illness develops within the brain over time.

DISCUSSION

This section of research and analysis explores the three most prevalent hypotheses surrounding the role of neuroscience in Alzheimer's disease, including the temporal lobe hypothesis, neurofibrillary tangles hypothesis, and amyloid plaque hypothesis. While they address different potential etiologies of Alzheimer's disease, they are closely related and together, highlight how the onset of this illness can affect multiple regions of the brain and contribute to cognitive decline.

TEMPORAL LOBE HYPOTHESIS

One theory regarding physiological causes of Alzheimer's disease postulates that temporal lobe atrophy leads to cognitive decline and subsequent memory loss. According to Killiany *et al.* (1993), "significant abnormality can be found in the temporal lobe of patients with only mild symptoms of AD," meaning that the onset of this disease can be marked in part by temporal lobe deterioration and the loss of neurons in this region of the brain can explain the lack of communication between neurons that allow for memory recall (p. 952). Determining where Alzheimer's

disease originates within the brain would allow for direct treatment; for instance, if medical professionals know that cognitive decline characteristic of Alzheimer's disease begins with temporal lobe atrophy, then they could immediately target this specific brain region for patients in the earlier stages of Alzheimer's disease. Moreover, Pettigrew *et al.* (2017) investigate both temporal lobe atrophy's relationship with Alzheimer's disease in its asymptomatic preclinical phase as well as the presence of biomarkers that might lead to temporal lobe atrophy itself. They found that high levels of amyloid plaques—further discussed later in this review—and p-tau proteins were associated with the greatest temporal lobe atrophy, but not the rate of atrophy, in both healthy controls and preclinical Alzheimer's disease patients; however, Alzheimer's disease patients experienced higher levels of both amyloid and p-tau in addition to subsequent temporal lobe atrophy (p. 442). These findings allow medical professionals to use brain-imaging technology to diagnose patients with Alzheimer's disease before it progresses by looking for decay in the temporal lobe as well as perform protein assays to determine amyloid and p-tau presence in this region. The ability to immediately diagnose Alzheimer's disease will not only allow for better patient care through early intervention, but also let researchers and physicians visualize changes in the brain over time with Alzheimer's disease onset by following patients from early- to late-stages.

NEUROFIBRILLARY TANGLES HYPOTHESIS
Another theory that addresses neural decay with Alzheimer's disease states that a buildup of neurofibrillary tangles—abnormal clusters that aggregate and fill the space that originally contained a healthy neuron—physically block and inhibit communication between neurons. As Alzheimer's disease progresses, these tangles grow in size and become increasingly damaging to memory and cognitive function. Bancher *et al.* (1989) explains that early tangles (Stage 1) are delicate bundles of fiber in the temporal lobe, which then mutate into mature tangles (Stage 2) that bundle together and can fill the entire neuron's cytoplasm, causing the nucleus to either shrink or dislocate. Lastly, in the final stage (Stage 3), they become large, loosely arranged bundles freely located without any connection to a neuron and are known as "ghost tangles". In this stage, the neuron dies, and bundles move into the space originally occupied by the affected neuron (pp. 93-4). As these tangles grow and kill off working neurons in the brain, neuronal signals in that region eventually stop altogether due to a lack of healthy neurons available for communication. Furthermore, Lewis *et al.* (2000) note that "neurofibrillary tangles (NFT) composed of the microtubule-associated protein tau are prominent in Alzheimer disease (AD)… Mutations in the gene (Mtapt) encoding tau protein cause frontotemporal dementia… thereby proving that tau dysfunction can directly result in neurodegeneration" (p. 402). This finding directly relates to the temporary lobe atrophy hypothesis in the tau protein's role in neuronal damage and resulting

cognitive decline in Alzheimer's disease patients. Detecting tau-protein associated neurofibrillary tangles in the beginning stages of Alzheimer's disease could allow for the early medical intervention necessary to slow its progression; using neuroimaging techniques to locate these tangles in a specific brain region would allow for treatment directly targeting bundles of neurofibrillary tangles to slow or even reverse Alzheimer's disease progression.

AMYLOID PLAQUE HYPOTHESIS

Another theory investigating Alzheimer's disease etiology posits that an adhesive substance known as Amyloid β-peptide (Aβ) forms plaques in the brain caused by random mutations in the gene coding for amyloid precursor protein (APP), leading to senility and memory loss. As Aβ accumulates in the synapse, where signals travel from neuron to neuron, allowing for various cognitive functions such as memorization and speaking (Hardy and Selkoe, 2002, pp. 353-4). When these plaques block the synapse, neurons are unable to communicate due to the loss of physical gaps available for signal transmission. This idea is further supported by the neurofibrillary tangles hypothesis in that Hardy and Selkoe (2002) note previous studies observing that mice that overexpressed the mutant APP gene experienced significant Aβ plaque buildup before neurofibrillary tangles formation, meaning that Alzheimer's disease most likely stems from an APP gene mutation leading to senile plaques in synapses between neurons that accumulate over time, eventually forming neurofibrillary tangles that kill and replace neurons. However, there are concerns with this hypothesis due to a lack of correlation between the number of amyloid plaques in the brain and severity of cognitive decline in Alzheimer's disease patients (p. 353). In other words, the amount of Aβ plaques in the brain is unrelated to degree of senility in Alzheimer's disease patients, making it difficult to eventually establish a causal relationship between these variables. If researchers can identify the cause of APP gene mutations and understand the association between Aβ plaques and Alzheimer's disease onset, then there would be potential for a preventative treatment inhibiting Aβ plaque buildup before it interferes with cognitive function.

CONCLUSION

Despite the overwhelmingly large number of patients and families burdened by Alzheimer's disease, most are unaware of the scientific findings behind its biological, physical, and emotional symptoms. It is vital to increase understanding of these relationships between neurology and Alzheimer's disease because it will not only inform them of the signs and symptoms to look for, but also allow them to obtain better patient care and increase quality of life for either themselves or an affected loved one through primary and secondary prevention. Additionally, educating the general population about this concept can also motivate other

researchers to further investigate potential underlying causes of and treatments for Alzheimer's disease.

The exact link between neuroscience and Alzheimer's disease has yet to be fully understood. While significant progress has been made, researchers and medical professionals are still exploring the etiology and progression of this illness. However, the temporal lobe, neurofibrillary tangles, and amyloid plaque hypotheses shed light on potentially promising treatments that involve directly targeting certain brain regions and could lead to an eventual cure. If researchers learn where specifically in the brain to attack Alzheimer's disease, medical professionals can then intervene with or even prevent its onset by knowing exactly where to look for neurological and physiological signs of Alzheimer's disease before it is too late.

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