Manipulating DREADDs to Develop a Novel Method to Non-Invasively Disrupt the Blood-Brain Barrier
(Technical project)
The Effect of Individualism vs Collectivism in USA and China on Alzheimer's and Dementia Rates
(STS project)

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that affects memory, cognitive skills, and, with significant disease progression, causes death. AD is currently the 7th leading cause of death in the United States. Hallmarks of AD include excess amounts of proteins in the brain and lost connections between neurons in the brain (*Alzheimer's Disease Fact Sheet*, n.d.). AD is the most common cause of dementia, which is an umbrella term used to describe a host of symptoms related to memory loss and decline in cognitive function. Between 60-80% of dementia cases are caused by AD (*Dementia vs. Alzheimer's Disease: What Is the Difference?*, 2021). Depending on the severity of disease progression, patients' day-to-day lives can change drastically. Mild AD effects can include getting lost, forgetting simple tasks, and personality changes. When the disease has progressed to moderate/severe, issues that often crop up include hallucinations, paranoia and an inability to communicate (*Alzheimer's Disease Fact Sheet*, n.d.).

Currently, it is estimated that costs associated with dementia (including Alzheimer's) in America will total $345 billion in 2023. Out of this figure, $87 billion will be paid out-of-pocket. If the current rates of AD and dementia persist, projections indicate that the health care costs associated with these afflictions will increase to $1 trillion annually by 2050 (*Alzheimer's Disease Facts and Figures*, 2023). As such, the overarching problem I am considering is how can we work towards lowering rates of AD and dementia?

The technical project will address the aspect of this sociotechnical problem concerning the limited number of drugs that are able to physically reach the brain and thus, be considered for AD treatment. By designing a novel platform to temporarily open the blood-brain barrier (a network of blood vessels that surrounds the brain) and allow drugs to enter brain tissue, we are directly working to lower rates of AD and dementia.

AD and dementia rates vary drastically across the world. The STS project will look at how individualistic vs collectivist (IC) mindsets held by the United States and China correlate with rates of AD and dementia in these countries. Individualistic societies esteem personal achievements and encourage people to prioritize their own needs over the needs of their community. In collectivist societies, individuals typically find meaning through their communities. Determining how this cultural dichotomy relates to varied AD/dementia rates could provide insight on changes people could make in their day-to-day lives regarding factors relating to IC (such as social ties) to minimize the risk of developing these diseases.

Patterns of social support for people of IC societies drastically differ. A growing body of evidence indicates that social support is related to both mental and physical health (Berkman, 1995). More specifically, there is a clear relationship between lack of social support and dementia rates (Salinas et al., 2022). I will explore this factor, among others, in greater detail to elucidate how IC cultures, like those of America and China, affect AD/dementia rates.

Technical Topic

The blood brain barrier (BBB) is a network of vasculature (blood vessels) that provides blood to the brain. All blood vessels are lined with cells known as endothelial cells. The endothelial cells of the BBB are connected by tight junctions (TJs) (Daneman & Prat, 2015). One of the main functions of the BBB is to protect the brain from foreign molecules and pathogens. It does this by creating a physical barrier to stop the movement of undesirable molecules into the brain.

While the BBB serves it purpose well, it also severely restricts the access of drugs/therapeutics to the brain. This is problematic because many diseases affecting the brain require therapeutics to be able to physically reach the brain tissue to be effective. This problem

manifests in the limited number of therapeutics for AD- only one drug is currently approved by the Food and Drug Administration (FDA) to treat moderate to severe AD (*Medications for Alzheimer's Disease*, 2023). The most common method that exists to temporarily open the BBB and allow therapeutics to enter the brain is focused ultrasound (FUS). This therapy requires the patient to travel to another site, making it difficult for people with mobility issues or lack of access to transportation. The specialty of the technique also drives up the cost of the therapy, making it less accessible to people of lower economic statuses. A study found that people treated with FUS for medication-refractory essential tremor paid an average of $21,438 more than those not treated with FUS (Li et al., 2019).

My group is utilizing designer receptors exclusively activated by designer drugs (DREADDs) to develop our platform. DREADDs are genetically engineered receptors that can be implanted in cells. A genetically engineered small molecule can then be administered to the cells expressing the designer receptor. The small molecule is designed to activate the engineered receptor and trigger a chain of events (Whissell et al., 2016). Currently, DREADDs are mainly used by neuroscientists to study neuronal connections. Because they are a relatively new technology, their application hasn't expanded past the academic realm (Roth, 2016). My capstone group and I are hoping to manipulate DREADDs to apply them to endothelial cells of the BBB with the aim of transiently creating openings (through loosening the tight junctions) in the BBB through which therapeutics can easily pass. 56% of oral drugs created since 1950 have a molecular weight greater than 400 Daltons (Leeson & Young, 2015). Only lipophilic molecules less than 400 Da are able to diffuse through the BBB (Pardridge, 2012). The limitations on molecules able to passively diffuse through the BBB clearly restrict the types of drugs that can be used for treatment of Alzheimer's and brain disorders in general. Looking at drugs currently

being used for brain disorders, only 6% out of the ~6,000 drugs in the Comprehensive Medicinal Chemistry database are active in the brain (Pardridge, 2012). If transient BBB openings were common practice and an easily available therapeutic option, this would open the door for many existing, FDA-approved drugs to be repurposed for various brain disorders, as well as allow for a wider variety of drugs to be developed for central nervous system (CNS) disorders.

My group and I are building on previous research into DREADDs. We are using a plasmid with the HA-hM4D gene inserted. The designer receptor that this gene expresses can be activated by the compound clozapine-*N*-oxide (CNO) (Armbruster et al., 2007). This DREADD falls under the umbrella of Gi-DREADDs, which are modifications of the G-alpha-I G-protein coupled receptor. Gi-DREADDs inhibit neuronal signaling by inhibiting adenylate cyclase, a precursor of cyclic adenosine monophosphate (cAMP) (*Addgene: Chemogenetics Guide*, n.d.). We are also building on existing knowledge about the role cAMP plays in modulating the tight junctions of endothelial cells of the BBB. It is largely accepted in the field that decreasing levels of cAMP causes the integrity of tight junctions to decrease, thus making the BBB more permeable (Viña et al., 2021). Previous literature has shown that cells expressing the hM4Di DREADD activated by CNO downregulate cAMP levels, with the level of downregulation directly related to dosage amount of CNO (Becnel et al., 2013).

One issue we might run into is cAMP not having the desired effect on our cells. More specifically, while most literature indicates a drop in cAMP levels increases BBB permeability, there are some studies that show the contrary is true (Viña et al., 2021).

STS Topic

While having dementia/AD in the family can increase one's risk of developing these diseases, the majority of AD and dementia cases are not inherited (*Is Dementia Hereditary?*,

n.d.). Major, non-genetic risk factors for developing AD and dementia include age, head injuries, lifestyle factors associated with cardiovascular disease, and some psychological issues (*Alzheimer's Disease - Causes*, 2018; *Dementia - Symptoms and Causes*, 2023). The prevalence of AD in the US for Americans aged 65 or older is around 10% (*What Is Alzheimer's Disease?*, 2023) while it is 3.9% in China for people 60 and older (Lv et al., 2023). Understanding what contributes to this difference is important to uncovering non-genetic factors that affect AD/dementia rates, which could in turn, help lower disease rates.

I hope to show how America's individualism vs China's collectivism contribute to this difference. A study analyzed data from 237 countries and found that self-reported levels of loneliness increased with a country's individualism (Barreto et al., 2021). Another study found that loneliness is a major risk factor for dementias, including Alzheimer's (Salinas et al., 2022). Some other factors associated with individualistic cultures include high mobility in relationships and weaker social ties (Lu et al., 2021). I will explore the relationship between these factors (and more) and AD/dementia rates in greater detail in my research paper.

The STS frameworks I plan to develop my project through are technological determinism and Hofstede's cultural dimensions. In Merritt Roe Smith's essay "Technological Determinism in American Culture," he argues that Americans subscribe to the belief that "changes in technology exert a greater influence on societies and their processes than any other factor" (Smith, 1994, p. 2). Smith critiques technological determinism, acknowledging the prevalence of the theory in American culture while explaining its shortcomings (Smith & Marx, 1994). I argue that Chinese society subscribes to the same viewpoint of technological determinism that America (as shown by Smith) does (Mahoney, 2023). Leaning on the idea that technological determinism (while flawed) is the dominant viewpoint in American and Chinese society, I posit that

technologies in place in both countries reinforce their approach to IC, which in turn, plays a hand in the varied rates of AD/dementia. I acknowledge that the individualism or collectivism core to these countries' identities have long-standing roots, and are by no means solely by-products of the technologies each country has embraced (Chan et al., 2022; Grant, 1986). Instead, I believe that technologies in each country promote the pre-existing values of IC. As such, technological determinism is a good framework to use to help understand the social factors (IC) that play into different AD/dementia rates. To further look at these social factors, I will utilize Hofstede's cultural dimensions. Hofstede's cultural dimensions theory is a framework used to understand cultural differences between countries (Hofstede, 2001; Hofstede & Bond, 1984). One of the dimensions used to quantify cultural differences is collectivism vs individualism (Wale, 2015). The individualism index is a way to quantify Hofstede's collectivism vs individualism dimension. The higher a country ranks, the more personal goals and autonomy are emphasized. Showing the marked difference between America and China are their individualism indices- the United States has an index of 91 and China has an index of 20 (Načinović Braje et al., 2019).

Research Question and Methods

The research question I plan to answer is how do differences in American individualistic and Chinese collectivist societies relate to the discrepancy between rates of AD/dementia in these countries?

I will research this project by looking at existing studies on AD rates in the United States and China. I will focus on epidemiological journals when I am searching for these studies. I will also conduct research on differences in these societies that arise as a result of individualism vs collectivism. For this research, I plan to look at research papers examining how these countries' attitudes towards society took form. I will also analyze papers that look at how individualistic or

collectivist societies influence the behaviors of citizens. For more information on how the STS frameworks provide background, I will identify omnipresent technologies in each country, and determine how they reinforce IC behaviors. I will lean on Hofstede's published works for information on how individualism and collectivism are defined and identified in societies.

Conclusion

For my technical project, my group and I plan to develop a novel therapeutic platform for temporarily opening the BBB with the goal of allowing drugs to reach the brain by utilizing DREADDs. For my STS project, I will analyze how the elements of individualism and collectivism present in USA and China (to different degrees) relate to varying rates of AD/dementia in these countries. If these deliverables are successfully completed, they will both work in favor of the goal of improving quality of life for people with Alzheimer's disease and dementia.

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