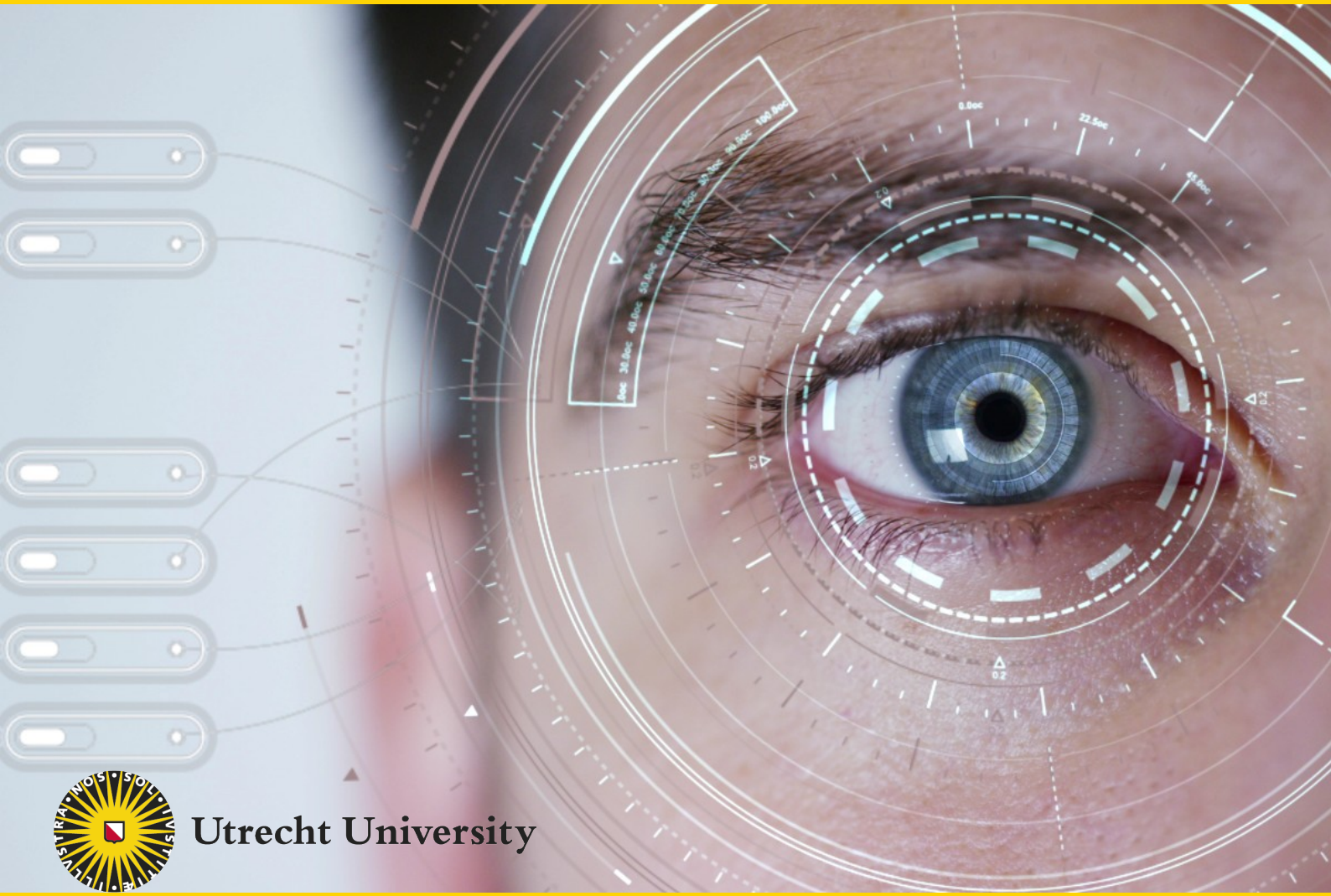
AI in Healthcare:

Eye-tracking as a Tool for Diagnosing Dementia

I. F. Murman

Bachelor thesis Artifical Intelligence
Utrecht University, July 2, 2021
7.5 ECTS
Thesis committee: S. Böing, MSc and Dr. S. M. Stuit



Utrecht University

AI in Healthcare:

Eye-tracking as a Tool for Diagnosing Dementia

by

I. F. Murman

to obtain the degree of Bachelor of Science in the field of Artificial Intelligence
at Utrecht University,

Student name:	Isabel Murman
Student number:	6419038
Project ECTS:	7.5
Project duration:	April 26, 2021 – July 2, 2021
Thesis committee:	S. Böing, MSc, Utrecht University, supervisor
	Dr. S. M. Stuit, Utrecht University, second assessor

Utrecht University

Abstract

Dementia is an umbrella term for the neurodegenerative process that underlies the progressive impairment in remembering, thinking, or making decisions that interferes with doing everyday activities. Diagnosing this disease is done using neuropsychological evaluation methods. However, these methods are time consuming and can lack sensitivity, which can make the diagnosis less reliable in some individuals and makes an early diagnosis difficult. Applications of eye-tracking for the diagnosis and possible tracking of dementia have been reviewed in order to determine to what extend eye-tracking based tests can help resolve these issues. A closer look into the findings suggests that eye-tracking is a valuable technique in combination with the visual paired comparison task to help diagnose impaired memory function, which in turn can help diagnose MCI or dementia. It also has great potential when combined with the antisaccade task to measure biomarkers such as oculometrics, which has shown valuable in the diagnosis of dementia because these eye movement deficits start early in the disease, even before cognitive deficits become noticeable. These eye-tracking based tasks thus show that eye-tracking can help diagnose dementia in an earlier stage, however, it is inconclusive whether eye-tracking could increase the reliability of a dementia diagnosis. Future research should thus involve a wider variety of oculometric biomarkers in order to possibly improve the reliability of eye-tracking. In addition, more research on improving eye-tracking algorithms could enable eye-tracking to be a more reliable method, and thus could make a dementia diagnosis using eye-tracking more reliable.

Keywords: dementia, MCI, eye-tracking, oculometrics, VPC task, AST

Preface

Following is the thesis ”AI in Healthcare: Eye-tracking as a Tool for Diagnosing Dementia”, a literary overview of the conceivable utilization of eye-tracking in diagnosing dementia. It has been written to fulfill the graduation requirements of the Artificial Intelligence bachelor program at Utrecht University. I was engaged in researching and writing this thesis from April to July 2021.

My research question was formulated under supervision of my supervisor, Sanne Böing. The research has allowed me to answer the question that I identified. Fortunately, Ms. Böing was always available and able to answer my queries.

I would like to thank Ms. Böing for her excellent guidance during this process. Without this I would not have been able to conduct this analysis.

To my fellow Artificial Intelligence students: I would like to thank you for your ideas and motivation as well. I also benefited from talking about issues with my friends. If I ever lost interest or motivation you helped me greatly.

I hope you enjoy your reading.

I. F. Murman
Utrecht, July 2021

Contents

1 Introduction

1.1. Introduction

Artificial Intelligence has developed greatly over the past years, and amid these developments different AI techniques have shown immense potential within the field of healthcare. The most well-known example of this is the potential use of robots to assist doctors and nurses during different procedures. But there are more uses for intelligent computer systems in healthcare than assisting during surgeries, as they can also diagnose impairments effectively. A study by Liu et al., 2019 has shown that the diagnostic effectiveness of deep learning Artificial Intelligent algorithms when diagnosing based on medical image can be as good as that of a medical professional, therefore showing that AI can be a useful tool in diagnosing different impairments or diseases. However, not all impairments or diseases are diagnosed using a medical image. Often diagnoses are instead made based on a set of behaviors or characteristics that are common in a certain impairment or disease. An example of this is when diagnosing dementia.

Being able to more reliably diagnose dementia using Artificial Intelligence will once more show the vast potential Artificial Intelligence has in reforming the healthcare industry. It opens doors for more research regarding the ability of AI to medically diagnose an impairment before evident symptoms appear. Furthermore, more research will facilitate the potential of improving the treatment options a patient has, as the process of choosing the right treatment requires processing large amounts of healthcare data to consider the symptoms, possible research mistakes, existing treatment methods, potential side effects, and much more. This process takes copious amounts of time and Artificial Intelligence could be a solution to improve this process further. As I illustrated, AI has great potential in transforming the medical industry. In this thesis I will consider the possible uses for Artificial Intelligence, specifically eye-tracking, when diagnosing different forms of dementia.

1.2. Symptoms of dementia

Before one can consider the use of eye-tracking when diagnosing dementia, it is first important to identify the different symptoms of dementia as these will help to understand the requirements the eye-tracking algorithm must meet in order to be able to successfully distinguish between healthy individuals and individuals with dementia.

Dementia is not a specific disease but is rather an umbrella term for the neurodegenerative process that underlies the progressive impairment in remembering, thinking, or making decisions that interferes with doing everyday activities. There are multiple forms of dementia but in this research I will limit my scope to the four most common forms of dementia, which together account for almost all dementia cases.

The most common form of dementia is Alzheimer's disease. This is a progressive neurological disorder which accounts for 65 percent of Dutch dementia cases (Staat van Volksgezondheid en Zorg, 2018). In this disease among the areas often damaged first are the hippocampus and its connected structures. This makes it harder to form new memories or learn new information (Alzheimer's Society, n.d.). The earliest symptom is therefore forgetfulness of recent events. Because Alzheimer's disease is a progressive disease this early symptom will eventually progress to forgetfulness of distant memories.

The key symptom of Alzheimer's disease, after all, is memory loss. Other symptoms that can occur in a later stage are personality changes, difficulty with walking and difficulty with talking. The patient will also have difficulty planning and reasoning, which leads to the worsening of executive functions. In later stages of the disease patients may forget how to perform everyday tasks, such as bathing or getting dressed (World Health Organization, 2020).

The second most common type of dementia is vascular dementia, accounting for approximately 22 percent of all Dutch cases of dementia (Staat van Volksgezondheid en Zorg, 2018). This form of dementia occurs after the brain's blood vessels have been damaged, resulting in a deficiency in nutrition and oxygen, which the brain needs to perform thought processes. This damage to the veins is caused by either a stroke that damaged a brain artery or a narrowed or chronically damaged brain blood vessel. The latter can for example be caused by diabetes, high blood pressure or aging. This damage can occur in different parts of the brain and is thus not tied to a specific localization, but it is often the result of widespread damage to white matter beneath the cortex (Alzheimer's Society, n.d.). Symptoms of vascular dementia are problems with reasoning, planning, judgement, memory and other thought processes. The symptoms are therefore very similar to those of Alzheimer's disease. People suffering from vascular dementia sometimes simultaneously suffer from Alzheimer's disease. This is because the abnormal protein deposits that are associated with Alzheimer's disease coexist with the blood vessel problems described earlier (Alzheimer's Association, n.d.).

The next type of dementia I will discuss is Lewy body dementia, which accounts for approximately 2 percent of all Dutch dementia cases (Staat van Volksgezondheid en Zorg, 2018). This progressive disease is caused by an abnormal deposit of alpha-synuclein in the brain. These deposits, which are the Lewy bodies, will in turn affect chemicals in the brain. These chemical changes can lead to Lewy body dementia. The Lewy bodies affect several different brain regions, the most important ones being the cerebral cortex, the limbic cortex, the hippocampus, the midbrain, the basal ganglia and the brain stem (National Institute on Aging, n.d.). Patients suffering from this type of dementia thus have both the more typical symptoms, like memory loss or other cognitive problems, as well as problems regarding movement, balance or sleep. Other possible symptoms are staring spells, hallucinations and confusion. Because Lewy body dementia is progressive the symptoms will worsen over time. This can result in severe dementia, aggressive behavior, an increased risk of falling, and eventually even death (Mayo Clinic, 2019).

The last form of dementia I will discuss is frontotemporal dementia. This is a group of uncommon brain disorders that primarily affect the frontal and temporal lobes of the brain and account for less than 4 percent of Dutch dementia cases (Staat van Volksgezondheid en Zorg, 2018). The affected brain areas are associated with personality, behavior and language, but memory is also affected. This form of dementia is often misdiagnosed as either a psychiatric problem or as Alzheimer's disease. One argument to differentiate this type of dementia from Alzheimer's disease is that frontotemporal dementia tends to begin between the ages of 40 and 65, which is younger than the onset of symptoms of most individuals suffering from Alzheimer's disease, which generally starts in their mid-60s (Mayo Clinic, 2021).

What these four dementia types have in common is the profound memory loss over time. This memory loss is already prevalent at the early stages of the disease. Thus, when attempting to diagnose dementia it is important that this memory loss can be measured well as it is a key symptom of the disease.

1.3. Neuropsychological evaluation

The way dementia is diagnosed today is through an approach called neuropsychological evaluation. This is a way of assessing a patient's brain function that yields inferences about the integrity of the brain. This information can then be used together with the assessment by a neurologist and a nurse practitioner to diagnose a patient with different cognitive impairments. Neuropsychological evaluation involves different standardized tests, which are typically pen and paper type tests. The goal of these tests when diagnosing dementia is to evaluate cognitive abilities such as attention, memory or processing speed, which are all impacted negatively by dementia. The scores that a patient achieves on these tests are then compared to the scores that a healthy individual with a similar demographic background is expected to achieve. The results of this for each of the tests make up the cognitive profile of a patient. The use of a cognitive profile increases the certainty of the diagnosis because one does not just look

at individual deficits, but at the combination of these deficits that together make up an impairment.

However, neuropsychological evaluation does have it's limitations. First of all, the tests are very time-consuming and are not always feasible or necessary in routine clinical practice. Secondly, a performance below a certain threshold is not always an indication of a dysfunction or underlying damage. A study by Larrabee, 1992 has after all already pointed out that a poor performance on neuropsychological tests can be the result of a variety of reasons apart from neurological disease. Examples of these reasons are psychiatric conditions such as depression or anxiety, inattentiveness, limited cooperation or poor motivation. A third limitation of neuropsychological evaluation is that the tests can lack sensitivity, meaning that early diagnosing of cognitive impairments such as dementia can be difficult. A study by Elkana et al., 2015 has suggested that highly educated individuals can obtain normal scores on cognitive screening tasks when experiencing subjective cognitive decline and difficulty in multiple cognitive domains. It is assumed that this is caused by the cognitive reserve of these individuals, which protects them from cognitive decline, and with that postpones the clinical display of dementia. Identifying subtle changes in cognition in these individuals thus requires more extensive resources, as the regular tasks lack sensitivity. This impedes identification of cognitive decline at its earliest stages. A study by Bahia and Viana, 2009 has also shown that neuropsychological evaluation tests commonly used in the medical office were unable to accurately distinguish between Alzheimer's disease and frontotemporal dementia, again showing a lack in sensitivity in neuropsychological evaluation.

1.4. Method

The three problems I illustrated show that neuropsychological evaluation is not a perfect method to diagnose dementia. The standard data used in these techniques are very old and the techniques themselves are mostly analog tests. Since technology has, like I mentioned earlier, already proven to be a useful tool in the medical field, it could potentially be used as a tool to help solve the previously described problems with neuropsychological evaluation. The goal of this literary study is therefore to analyze different eye-tracking techniques to determine how these could be used to help diagnose dementia in a clinical setting to make the current evaluation practices more reliable or sensitive. The research question that will be central is 'To what degree can eye-tracking practices be of additional value in diagnosing dementia?'.

In order to answer this question I conducted literature searches. The key and index words were as follows: dementia, eye-tracking, early detection, early diagnosis, mild cognitive impairment, longitudinal studies, cognitive assessment, VPC task, antisaccade task. The databases used in order to search for the studies were PubMed, PsycINFO and Google Scholar. Inclusion criteria used for the studies were that the studies had to be in English and that in all experimental studies besides patients also healthy age matched controls were present. All studies were limited to human subjects and were published from 2001 to 2020 and I searched in the period of May 2021 to June 2021.

The first part of the study focuses on the determining whether eye-tracking could be beneficial in diagnosing dementia earlier. To determine this I will hypothesize about the symptoms that dementia could have in an earlier stage. From here I will look at the possibilities of using eye-tracking to diagnose dementia in this earlier stage using these symptoms. Subsequently I will explore in what cases traditional neuropsychological evaluation fails to diagnose dementia early and effectively, and determine whether eye-tracking techniques could be a reliable addition or alternative in these situations. This will provide an extensive overview of the additional value that eye-tracking could provide with regards to both increasing the sensitivity and the reliability of diagnosing dementia.

2

Mild Cognitive Impairment

2.1. Preclinical stage of dementia

When considering how dementia can be diagnosed in an early stage it is first and foremost important to determine how such a stage would look.

Inasmuch as the neuropathological changes of dementia start slow, the disease is not apparent right away. It is thus not possible to diagnose an individual with dementia immediately after the onset of the disease. However, since dementia is progressive these changes eventually do become large enough where they start to disrupt daily functioning. At this point the diagnosis of dementia can be made using neuropsychological evaluation. Nevertheless, before this diagnoses is made there are already cognitive signs and changes in the brain, these changes just went unidentified. This denotes the existence of a preclinical stage of dementia.

To illustrate this principle further I made the graph that is shown in Figure 2.1. This graph shows the cognitive and functional decline an individual suffers from as their dementia progresses and follows a quadratic curve (Mitnitski et al., 1999 and Haaksma et al., 2018). The graph in Figure 2.1. is split up in two parts: an orange part and a white part. The orange part of the graph is the preclincal stage and is also denoted by the number 1, and the white part is the clinical stage which is denoted by the number 3. The preclinical stage and the clinical stage are separated by the moment where there is sufficient evidence to diagnose dementia with adequate reliability using neuropsychological evaluation, which is denoted by the number 2 in the graph. In area 1 of the graph, the preclinical stage, an individual is already suffering from dementia but this goes unknown as the disease has not yet progressed far enough to be diagnosed using neuropsychological evaluation. Considering that dementia is a progressive disorder, we can deduce that the symptoms in area 2 of the graph are mostly a progressed version of the symptoms in area 1. This denotes that the symptoms present in the clinical stage of dementia would largely already exist in this preclinical stage, but just less severe. Thus to determine what the symptoms of the disease could look like in the preclinical stage, we must take the symptoms from the clinical stage and hypothesize what a regressed version of these symptoms would look like.

The key symptom of the clinical stage of dementia, as described in the introduction of this thesis, is a severe decline in cognitive abilities, such as memory. I believe that the decline in cognitive abilities would already be present in the preclinical stage of the disease, however the cognitive abilities would presumably be less impaired than they are in the clinical stage of dementia. I theorize that possible symptoms of this preclinical stage of dementia might be that an individual would have difficulty remembering details from recent conversations, or that they would rely on a notebook or calendar in order to schedule. This decline in cognitive abilities would probably be severe enough that it would not go unnoticed, but it would not be severe enough that the independence or daily function of the individual are affected much, since if early dementia were that severe it would not go undiagnosed. Because dementia is progressive, the more the disease progresses the more severe this loss of cognitive abilities will become until we reach the point of area 2 in the graph, where there is sufficient evidence to make an adequately reliable diagnoses of dementia.

The examples of how the early stage of dementia can manifest itself that I hypothesized previously show a decline in cognitive ability, but not yet to a degree that the daily function of the individual is

affected. These symptoms sound similar to those of mild cognitive impairment (MCI).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines MCI as an impairment characterized by a noticeable deterioration of cognitive function beyond what is expected based on age (DSM-5, 2017). This deterioration is noticeable, but is not significant enough to affect the individual's ability to carry out everyday tasks. From the overlap between this definition of MCI and the notion of the preclinical stage of dementia I described in the previous paragraphs, the question whether MCI might be related to the preclinical stage of dementia follows. I will discuss this idea in the rest of this chapter.

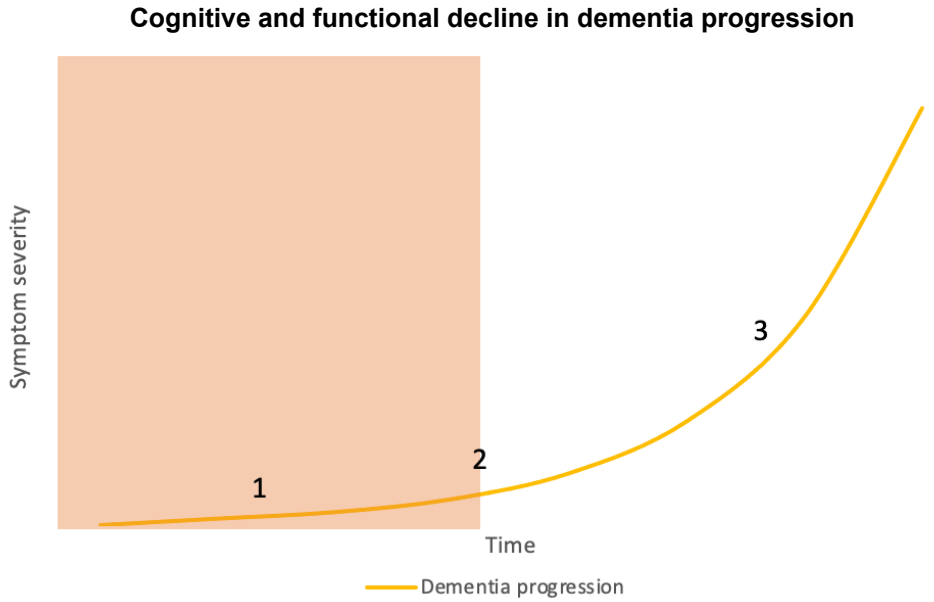


Figure 2.1: Dementia progression of symptoms from the onset of the disease onward, denoted by the arbitrary numbers 1 (preclinical stage), 2 (moment of diagnosis using neuropsychological evaluation) and 3 (clinical stage)

2.2. Relationship between MCI and dementia

2.2.1. Great risk of developing dementia for MCI patients

Many researchers have studied the resemblance between MCI and the preclinical stage of dementia to determine whether a relationship between the two exists. These studies show that there is indeed a relationship between MCI and dementia.

The first research suggesting such a relationship is by Petersen et al., 2001. This study is a literary overview that examined 74 longitudinal studies to determine whether individuals with MCI had an increased risk of developing dementia relative to the general age-matched population. The results showed that in the general population the progression rate to dementia is 0.2 to 3.9 percent, while in individuals with MCI this rate is substantially higher, namely between 6 and 25 percent per year. This suggests that individuals suffering from MCI have an increased risk of developing dementia later on when compared to the general population.

Another study by Bruscoli and Lovestone, 2004 also examined different literature about this topic. They used 19 longitudinal studies that addressed the conversion rates from MCI to dementia. From this they concluded that this rate of conversion from MCI to dementia was approximately 10 percent, however large differences between studies did exist, which was mostly caused by differences between the sources of subjects between studies as well as heterogeneity within studies cognitive testing. Even though large differences between studies were found, the data still strongly supports the hypothesis that MCI predicts conversion to dementia, again showing a relationship between the two.

A study by DeCarli et al., 2004 confirmed this hypothesis again. They concluded that MCI patients have an increased risk of developing dementia after a longitudinal study of approximately 3 years using 51 participants with MCI took place. 33 percent of these participants developed dementia in this time span. This again shows that there exists a relationship between MCI and dementia.

2.2.2. Greater risk of developing dementia for aMCI patients

The above studies discussed whether a relationship exists between MCI and dementia, but they did not take into consideration that there are different types of MCI, and thus that this could affect the progression rate to dementia. The first study that I will discuss that did research the influence of the heterogeneity of MCI on dementia progression rates is by Fischer et al., 2007. In this study Fisher et al. differentiated between two MCI subtypes: amnesic MCI (aMCI) and non-amnesic MCI (naMCI). They studied whether the rates of progression from MCI to Alzheimer's disease differed between patients suffering from aMCI compared to those suffering from naMCI. Fisher et al. found that in their study 48.7 percent of aMCI patients converted to Alzheimer's disease, while only 26.8 percent of naMCI patients converted to Alzheimer's disease. They concluded this using a total of 141 MCI patients. The results of this study shows that even though naMCI patients still have a high risk of developing dementia, this risk is increased further in aMCI patients. Another study by Yaffe et al., 2006 shared this same conclusion. The researchers in this study wanted to know whether the heterogeneity of MCI influences its clinical course. They studied this by following 327 MCI patients longitudinally. After a follow-up of three years they determined that aMCI patients were more likely to progress to dementia than naMCI patients were.

This difference in progression rates found in these studies can be explained using a study by Csukly et al., 2016. In this study the brains of patients with aMCI, naMCI and healthy controls were compared using structural MRI. From this comparison Csukly et al. were able to draw the conclusion that the sizes of the hippocampus, the entorhinal cortex and the amygdala were decreased in patients suffering from aMCI in comparison to those suffering from naMCI and to the control participants. Furthermore, the cortical thickness of the entorhinal cortex, the fusiform gyrus, the precuneus and the isthmus of the cingulate gyrus were significantly decreased in patients suffering from aMCI relative to those suffering from naMCI and healthy controls. These structural changes are associated with the increased deterioration in memory in aMCI patients compared to naMCI patients. This increased detoriation in memory can be the reason for the heightened dementia risk in aMCI patients. These conclusions show that even though all MCI patients have a high risk of developing dementia, this risk is increased even further in aMCI patients, meaning that it is important to be able to differentiate between aMCI and naMCI patients in order to effectively know what group has the highest risk of developing dementia and thus could benefit most from further testing.

2.2.3. MCI as a possible precursor to dementia

The studies I described all show that individuals living with MCI have an increased risk of suffering from dementia later on. This shows that there is most definitely a relationship between MCI and dementia. This relationship is however not the same as MCI being a precursor to dementia and it should not be mistaken for one.

The reason for this can be found in the definition of MCI. The definition that DSM-5 gives is rather broad and does not specify a definite underlying cause. Furthermore, there is no mention in this definition that MCI has to be progressive. This means that there are cases where MCI does not progress further or can even be reversible. A study by Gauthier and Touchon, 2005 gave criticism on the popular notion that MCI is a precursor to dementia because of these reversible causes, such as depression, upper airway obstruction and a variety of metabolic, nutritional, or sensory impairments. They mentioned that these reversible causes make a diagnosis of MCI as a preclinical stage of dementia in such individuals inaccurate. I agree with Gautier and Touchon on the notion that MCI is not a precursor to dementia. A key part of dementia is that it is a progressive impairment, and because MCI is not per definition progressive I do not believe it to be a phase of dementia.

2.3. Cognitively monitoring MCI patients

Even though it is inaccurate to refer to MCI as a precursor to dementia, it may very well be the case that virtually all dementia patients have had MCI in the earliest stages of their impairment, making MCI useful when diagnosing dementia. This can be explained by looking at the definitions of both dementia and MCI: dementia is an umbrella term for impairments resulting in the progressive deterioration of cognitive function that interferes with doing everyday activities, and MCI is an impairment where there exists a noticeable deterioration of cognitive function beyond what is expected based on age. In the deterioration process of dementia the decline in cognitive function will inevitably progress from unnoticeable to noticeable. At that point the patient will have met the above mentioned criteria for MCI, with

the underlying cause of the impairment being dementia. This means that according to the definitions of both dementia and MCI it is likely that dementia patients suffer from MCI in the early stages of their disease. This explanation in combination with the evidence of the existence of a relationship between MCI and dementia as described earlier strongly suggests that it is beneficial to cognitively monitor MCI patients for cognitive and functional decline due to their increased risk for subsequent dementia. This benefit could be most significant for the group of aMCI patients as their risk of progression is even higher than that of other MCI patients.

The idea of cognitively monitoring MCI patients for cognitive and functional decline leads to new possibilities with regards to diagnosing dementia in an earlier stage. By cognitively monitoring these patients who have an increased risk for developing dementia it is possible to notice further deterioration expeditiously and thus diagnose dementia earlier than we can today.

3

Eye-tracking to diagnose dementia in an earlier stage

3.1. Eye-tracking based tasks to diagnose MCI and dementia

The relationship between MCI and dementia makes a timely and effective MCI diagnosis important, as this facilitates cognitive monitoring which could be crucial in order to diagnose dementia earlier. There exists evidence that different eye-tracking based tests could be useful methods to achieve this goal. An overview of general information about the participants, criteria and conclusions of the studies that provide the evidence that will be discussed in this chapter can be found in Table 1.

3.1.1. Eye-tracking based visual paired comparison task

The first eye-tracking based test that could be used to diagnose MCI or dementia is the visual paired comparison task (VPC task). This is a recognition memory task that is used to assess the relative amount of time a participant spends viewing a novel image compared to a previously shown image. In this task the important characteristic of healthy individuals is that they tend to focus substantially more on the novel image than the familiar one. By comparison, individuals suffering from a memory impairment could be characterized by a more equal distribution between the novel and the familiar images, as these individuals can have difficulty remembering that they had seen the familiar image previously. This makes the VPC task very well suited for measuring memory function, which is why it is an interesting task to use in order to help diagnose dementia.

In a VPC task participants are instructed to view two images. After a few seconds the monitor they viewed these images on becomes dark for some time, after which two pictures are again shown, this time one picture is identical to the ones shown earlier and the other one is novel. By combining this test with eye-tracking it is possible to accurately compare the proportion of time spend on viewing each image.

The study by Crutcher et al., 2009 used a VPC task combined with infrared eye-tracking in order to determine whether eye-tracking can be used as a tool to help diagnose MCI. Eye-tracking showed that after the screen went dark for 2 minutes control participants viewed the novel picture above 70 percent of the time, while MCI patients viewed the novel picture only 53 percent of the time and the familiar picture 47 percent of the time. This shows that patients with MCI had difficulty remembering that they had seen the familiar image already and thus treated it as a novel one. With this research Cruther et al. concluded that eye-tracking is a useful tool when assessing both normal and impaired memory function. This conclusion supports the notion that eye-tracking can be used to help diagnose MCI, and with that possibly help diagnose dementia in an earlier stage.

This conclusion was reinforced by a study by Gills et al., 2020. They aimed to examine the relationship between a brief eye-tracking based VPC and standard neuropsychological evaluation, as well as determine the ability of the VPC task to differentiate between cognitively normal individuals and individuals with MCI. In order to examine the relation between the eye-tracking based VPC results and those of standard neuropsychological evaluation they compared results from the VPC task, Montreal Cognitive Assessment (MoCA), Digit Symbol Coding test (DSST) and NIH Toolbox Cognitive Battery

(nihtb-cb). It was found that the VPC results are related to those of the neuropsychological evaluation tests. Furthermore, eye-tracking based VPC was able to reliable predict the cognitive status of individuals. Gills et al. also mentioned that because the VPC task can be taken remotely in a user's home, it enables more scalable longitudinal assessment and tracking of cognitive changes. This could make the eye-tracking based VPC task useful when cognitively monitoring in order to diagnose dementia earlier.

The last VPC study I will discuss used a portable eye-tracking based VPC task (P-VPC task). This study by Whitehead et al., 2018 was again able to observe that individuals with dementia more evenly distribute their time between the familiar and novel image when compared to healthy controls, which once more suggests that the VPC may be a potential tool for screening memory decline.

These studies suggest that eye-tracking based VPC is possibly an adequate tool to both measure memory function in order to help diagnose MCI or dementia, as well as help cognitively screen MCI patients to diagnose dementia in an earlier stage.

3.1.2. Eye-tracking based antisaccade task

The second eye-tracking based test that could be used to help diagnose different types of MCI as well as dementia is the antisaccade task (AST). In this task participants try to suppress their reflexive urge to look at a distractor, which is a visual target that appears in the visual field of the individual. Instead, the participants are instructed to look away when the distractor appears. The frontal lobes and basal ganglia help top-down inhibition of an automatic saccade, which is a crucial step in this task (Munoz and Everling, 2004). As described in the introduction of this thesis, dementia patients can suffer from damage to these areas, which is why they can find it more difficult to suppress the automatic saccade and thus why they can perform worse on the AST than healthy controls. Another study suggesting that eye movement deficits can be an important marker for diagnosing dementia is by T. Crawford et al., 2005, as they concluded that eye movement deficits can develop early in the course of Alzheimer's disease, even before the cognitive deficits that neuropsychological evaluation is dependent on are apparent. This conclusion also shows the potential of eye-tracking based tests, such as the AST, to help diagnose dementia earlier.

A study by Wilcockson et al., 2019 uses the AST to study whether eye-tracking could be used to differentiate between patients suffering from aMCI and those suffering from naMCI. They did this because, as mentioned in the previous chapter, aMCI patients have an increased risk of developing dementia. It is thus critical to be able to differentiate between aMCI patients and naMCI patients in order to know what patients could benefit most from cognitive monitoring. The results of the AST showed that the number of reflexive saccades to the target location, which the participants were inhibiting, was lowest in the control patients and naMCI patients, and highest in aMCI patients and Alzheimer's disease patients. The same order of performance was found in the time it took participants to correct the reflexive saccade. These results showed that individuals suffering from aMCI performed worse on the AST than those suffering from naMCI or the healthy controls. From this research Wilcockson et al. concluded that AST is a promising biomarker for dementia and that it can be used as an additional prognostic tool for predicting which people with a diagnosis of MCI are more likely to progress to dementia as AST can be used to differentiate between aMCI and naMCI.

A study by Chehrehnegar et al., 2021 also aimed to use an eye-tracking based AST to differentiate between aMCI and naMCI, for the same reasons as described earlier. In this research Chehrehnegar et al. measured saccade reaction time, saccade errors, saccade omission and uncorrected saccades. Chehrrehnegar et al. used poor performance on these parameters as markers of both executive function deficits and visual attention deficits. The findings showed that the aMCI patients had more errors, more omissions, and fewer corrections than the control group. These results show both inhibitory control and working memory deficits in patients with aMCI. This again shows that eye-tracking based AST is a suitable test to differentiate between aMCI and naMCI, making it a suitable cognitive marker in aMCI.

The research by Crawford et al., 2019 also used eye-tracking based AST. In their study they found, as predicted, an increase in the frequency of AST errors in Alzheimer's disease patients and MCI patients when compared to the healthy controls. These results once more show that the AST can be used to help diagnose both MCI and dementia.

The conclusions of these studies suggest that eye-tracking can also be used in combination with the AST in order to differentiate between aMCI and naMCI patients, as well as to help diagnose MCI

and dementia, again meaning that eye-tracking offers possibilities with regard to the earlier diagnosis of dementia as well as tracking the progression of the disease.

3.1.3. Eye-tracking based task for rapid assessment of MCI and dementia

Next, I will discuss a study suggesting that eye-tracking can be a suitable method for a rapid 3 minute assessment of MCI and dementia. This study by Oyama et al., 2019 aimed to search for an alternative for neuropsychological evaluation using eye-tracking, and to do this they developed a cognitive assessment utilizing eye-tracking technology. In this assessment the individual views a series of short movies and pictures displayed on a monitor while their gaze points are recorded by an eye-tracking device. The entire process of this assessment takes less than 3 minutes, which is substantially shorter than traditional neuropsychological evaluation tests, which can each take over 10 to 20 minutes to perform. The movies and pictures make up a series of tasks designed to assess specific neurological domains, such as deductive reasoning, working memory, attention and memory recall. Each task consists of multiple images, including a correct answer, which is referred to as the target image, and distractors. The participants are instructed to identify and focus on the target image. The cognitive score of each participant was determined from the gaze plot data by measuring the relative duration that the participant fixated on the target image. The average of these percentages for each task make up the cognitive score of the individual. All participants also received a cognitive score using neuropsychological tests such as the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Frontal Assessment Battery (FAB), and Clinical Dementia Rating (CDR) in order to determine how well the eye-tracking method performed. After evaluating the correlation in cognitive scores between the neuropsychological evaluation method and the eye-tracking method, it was concluded that the eye-tracking method showed a good diagnostic performance in detecting cognitive impairments in patients with MCI and dementia. The correlation between the neuropsychological evaluation scores and eye-tracking scores does not necessarily imply that neuropsychological evaluation can be replaced by this short assessment, however it could mean that eye-tracking can assist neuropsychological evaluation in for example tracking the progression of MCI or dementia, or it could be used in cases where individuals are not able or willing to undergo long testing. Oyama et al. also noted that subjects who had a CDR score of 0.5, and thus were at a high risk of developing dementia, had significantly lower scores in the eye-tracking assessment versus the neuropsychological assessment, suggesting a high sensitivity for detecting patients in a very early stage of dementia. The eye-tracking assessment also achieved high diagnostic performance for diagnosing MCI, which suggests again that the assessment Oyama et al. developed is very useful for diagnosing dementia in an early stage. The last noteworthy conclusion that was drawn during this experiment was that neither a patient's age nor the severity of their cognitive impairment affected the recording efficiency of the eye-tracking assessment.

3.2. Benefits of using eye-tracking based tests

The studies I described all provide evidence that eye-tracking can be used together with different tests, such as the VPC test or AST, to diagnose MCI or dementia. There are different advantages to using eye-tracking over its alternatives. The first advantage is that eye movement is a biomarker that is able to diagnose dementia in the earliest stages and is not invasive nor expensive. Alternatives that can diagnose dementia in an early stage as well involve lumbar puncture or a cerebrospinal fluid sample, which are both very invasive techniques, or it can involve neuroimaging which is expensive (Wilcockson et al., 2019). The next advantage of using eye-tracking as shown in the study by Oyama et al., 2019 is that traditional neuropsychological tests, such as MMSE and ADAS-Cog, take longer than 10 to 20 minutes to complete, which is substantially longer than the 3 minutes that the eye-tacking assessment took in their study. The last benefit of eye-tracking I will discuss is that the tasks used can be customized for specific aims and requirements: testing memory and memory recall can be useful for diagnosing dementia because this is characterized by memory loss, but other cognitive impairments may be characterized by other symptoms, and thus require other tests. Eye-tracking is a technique that can be customized to measure eye movement in many different tasks in order to test for different symptoms (Oyama et al., 2019).

Table 1: Overview of eye-tracking studies used

Study source	Number of experimental participants	Number of total participants	Mean age, y	Criteria	Eye-tracking test used	Conclusion
Chehrehnegar et al., 2021	40	120	66.3	aMCI	AST	Eye-tracking based AST can be used to diagnose aMCI as the saccade behavior of these patients is characterized by more errors, more omissions, and fewer corrections compared to controls
Crawford et al., 2019	107	202	69.5	MCI or dementia	AST	There exists an increase in the frequency of AST errors in dementia and MCI patients when compared healthy controls
Crutcher et al., 2009	4	25	67.5	MCI	VPC	Eye-tracking based VPC can assess both normal and impaired memory function
Gills et al., 2020	44	55	56.4	MCI	VPC	Eye-tracking based VPC can reliably predict cognitive status while demonstrating high test-retest reliability
Oyama et al., 2019	53	80	74.0	MCI or dementia	Own test	The rapid eye-tracking assessment used achieved high diagnostic performance and sensitivity of MCI and dementia
Whitehead et al., 2018	59	171	50.9	Dementia	Portable VPC	Differences in performance on the portable eye-tracking based VPC task are observed in dementia patients, which suggests that this may be a potential tool for screening memory decline
Wilcockson et al., 2019	89	249	71.2	aMCI or naMCI	AST	AST can be used to differentiate between aMCI and naMCI patients

4

Eye-tracking to diagnose dementia more reliably

4.1. Eye-tracking in special cases

Besides diagnosing dementia in an earlier stage, eye-tracking could also have practical use in diagnosing dementia more reliably. As mentioned in the introduction of this thesis, there are scenarios in which traditional neuropsychological evaluation could fail to diagnose a patient with dementia, but there are more factors impacting the reliability of the diagnosis than the ones mentioned there. This chapter focuses on providing an overview of the cases where eye-tracking based techniques could increase the reliability of standard neuropsycholical evaluation, as well as consider the situations in which it cannot accomplish this.

The first problem that affects the reliability of neuropsychological evaluation as mentioned in the introduction of this thesis is that poor performance on neuropsychological tests is not always the result of neurological disorder, as psychiatric conditions such as depression or anxiety, inattentiveness, limited cooperation or poor motivation can also negatively impact the results an individual will receive (Larrabee, 1992). These factors affect the reliability of neuropsychological evaluation, but they also impact the reliability that eye-tracking has when diagnosing dementia. A study by Carvalho et al., 2014 has concluded that patients with depressive disorder have abnormal eye movement indices, which when performing the eye-tracking based AST results in poor saccade latency, error rates and correction rates, which is similar in dementia patients, showing that eye movement would not be a reliable biomarker of diagnosing dementia in these cases. Furthermore, according to a study by Li et al., 2016 a core symptom of depression is the impairment of cognitive functions, meaning that depression also impacts cognition, memory, attention, recognition, and recall. This implies that eye-tracking methods to test for the deterioration of these cognitive functions would also fail to be able to diagnose dementia reliably, as the found results could also be the result of psychiatric conditions. Limited cooperation, inattentiveness or poor motivation can also impact the results of an eye-tracking study, making the method less reliable. A study by Scinto et al., 1994 suggested that a limited attention span can interfere with oculomotor control. This means that just as in neuropsychological evaluation, limited attention can affect the results of the dementia diagnosis when using eye-tracking based tests as they rely on oculomotor control. These studies imply that the first problem of neuropsychological evaluation as illustrated in the introduction would not be solved by using eye-tracking based tests.

The other problem that I mentioned regarding the reliability of neuropsychological evaluation is that they can lack sensitivity. To reiterate, a study by Elkana et al., 2015 suggested that highly educated elders require extensive resources to identify their cognitive decline at its earliest stages, neuropsychological evaluation tests lack the needed sensitivity, making it difficult to diagnose dementia in an early stage in this population. I believe that eye-tracking could be a solution to this problem because it does not rely on visible cognitive loss in order to diagnose dementia, but instead uses eye movement deficits such as the increase in saccade errors in dementia patients, which are visible even before cognitive loss becomes noticeable (T. Crawford et al., 2005). If a patient suffers from dementia, their eye movement would be affected, and this cannot be masked by intelligence in the way that impaired cognition

can. This denotes that eye-tracking could be a reliable addition to neuropsychological evaluation when diagnosing dementia in this special population.

4.2. Eye-tracking in later stage dementia

A third problem that could impact the reliability of neuropsychological evaluation is that it relies on verbal or motor responses. In the later stages of dementia both the motor and verbal responses of a patient can be impaired, making neuropsychological evaluation tests to track the decline of the patient challenging and often not possible (Bueno et al., 2019). In this situation eye-tracking can be a useful alternative because it can be used help track dementia without requiring motor or verbal responses. This alludes that eye-tacking based tests can be used to track dementia progression over time effectively and reliably even when patients have impaired motor or verbal responses.

4.3. Eye-tracking as an objective method

The reliability of neuropsychological tests are affected by the fact that they are not objective. They have to be executed by a highly trained examiner in order to obtain reliable scores. In the study by Oyama et al., 2019 it was hypothesized that because examiners have a varying level of proficiency with these tests, their application can be affected by the skill of the examiner. A study by Whitehead et al., 2018 showed that eye-tracking tests could be more objective. They showed this by contrasting P-VPC metrics against the MoCA in healthy adults and adults with dementia to assess the validity and reliability of the P-VPC as an indicator of memory function across age and to determine the P-VPC's use as a measure in clinical diagnosing. They found that when compared to the MoCA, P-VPC scores did not differ based on education or the individuals native language. This shows that the P-VPC task, which relies on eye-tracking, can be a more objective assessment than the MoCA, reinforcing the idea that eye-tracking could be a more objective way of diagnosing dementia than neuropsychological evaluation. This conclusion was fortified again in a study by Marandi and Gazerani, 2019. This study aimed to give the potential impacts of using characterizing features of eye movements and oculometrics as examples of objective biomarkers in the context of aging. The findings of this study showed that eye-tracking is a powerful tool to provide objective biomarkers in the form of oculometrics, such as amplitude, duration, velocity, frequency, acceleration, deceleration, latency and saccade peak velocity, just to name a few, which can assist in diagnosing neurodegenerative disorders, like dementia. Furthermore, eye-tracking can provide objective biomarkers that can help in the follow-up of disease progression or to help determine the therapy effectiveness. Marandi and Gazerani did also name some possible weaknesses in the study of eye-tracking that could limit the reliability of the biomarkers. They mentioned that in order to rely on oculometrics as an objective biomarker of neurodegeneration, it is important to have a broad view on the possible variability of oculometrics. They found that this variability can be caused by the use of caffeine, nicotine and drugs. Oculometrics may also change because of fatigue, emotional states, cognitive load and environmental factors. Another source of variability can be measurement errors, which can either be caused by humans when they record or analyze the data, by technical deficiencies in the eye-tracking device, or by the inability of the patient to execute the task properly. It is for example difficult to use eye-tracking on individuals with glasses or contact lenses because calibration is often needed which makes the process take longer and makes eye-tracking more prone to human errors than previously thought. These errors should be taken into consideration when interpreting eye-tracking results, again making the method less reliable. Since dementia is a disease most common in individuals of an old age, and these individuals often wear glasses or contact lenses, this is a common problem.

Overall, there is evidence suggesting the possibility of increasing the reliability of the dementia diagnosis using eye-tracking, however this evidence is not conclusive. It is not a topic studied much so far, making the conclusions less reliable, and there are certain disadvantages to using eye-tracking as well as problems it shares with neuropsychological evaluation, as mentioned above. It is possible that eye-tracking can make the diagnosis more reliable in a specific group of the total population, but this does not make the tool as a whole more reliable. However, eye-tracking techniques develop quickly so an eye-tracking technique that improves the reliability of a diagnosis could be developed in the future as the tool has great potential.

5

Discussion

The results of this study have shown that eye-tracking has additional value when diagnosing dementia as it can help diagnose this disease in an earlier stage. It is also possible that the reliability of diagnosing dementia using eye-tracking could improve in the future, as the results of an eye-tracking diagnosis are dependent on the quality of the algorithms used. To explain, as algorithms develop further they can improve the sensitivity of eye-tracking and could possibly eliminate some issues which cause reduced reliability.

Eye-tracking thus depends on the techniques used in the development of its algorithms. As more research and development takes place on improving the techniques that underlie these algorithms, the more eye-tracking can progress. Different AI approaches could be used to to improve the algorithms used in eye-tracking. Examples of such techniques are machine learning or cloud computing. A literary study by Klaib et al., 2021 has provided an extensive overview of the use of these techniques in order to develop eye-tracking applications. This study concluded that using machine learning is an important aspect in evolving eye-tracking applications, because it enables these application to learn from existing data, make better decisions, to be flexible in use and to eliminate the need to manually re-calibrate the tracker during the eye-tracking process. They also mentioned that cloud computing could improve the usability of eye-tracking, as combining eye tracking with cloud computing will allow efficient data storage, sharing, processing, modeling, and evaluation, which overall makes eye-tracking less time-consuming even when using large amounts of data. Furthermore, when compared to more traditional event-driven algorithms such as the ones described by Nyström and Holmqvist, 2010, the algorithms based on machine learning and cloud computing result in more accurate detection results. These modern techniques thus have the ability to improve eye-tracking algorithms further, which in turn could improve the reliability and sensitivity of a dementia diagnosis.

However, there are some limitations to this. The accuracy of an eye-tracking system using machine learning techniques, such as for example regression, neural networks, naive Bayes classification or support vector machines, depends heavily on the quality of the collected data which in turn depends on the number of subjects involved. It is thus important to have elaborate training sets, which requires many subjects, in order to capture heterogeneity. Meaning that if the dataset used to train on is small or in any way biased or inaccurate, the model made could provide poor results.

Overall, the algorithms used in eye-tracking impact the results of this technique. As more research about machine learning is done to make the techniques even more efficient and reliable, it is expected that the sensitivity or reliability of an eye-tracking based diagnosis could improve for dementia patients. The improvement in algorithms alongside the possible development of different tests that can be used with eye-tracking could have important implications for both the field of healthcare as well as the field of Artificial Intelligence.

Firstly, diagnosing dementia in an earlier stage has important implications in the field of healthcare. Recently, Aduhelp was approved as a medication to treat new cases of Alzheimer's disease. This news gives hope that as more research is done, more medications to help treat dementia become available. In order to make this a reality patient recruitment for clinical trials for drug development is vital. Diagnosing dementia in an earlier stage can increase the efficiency of patient recruitment. When attempting to diagnose patients earlier using eye-tracking there are some challenges that need to be

faced first. One of these challenges is that some drugs used to treat neurodegeneration patients are known to affect the oculomotor function and thus could potentially interfere with eye-tracking results. An example of such a drug is dopamine medication (Pinkhardt et al., 2012). Another possible issue with using eye-tracking that has to be solved in order for it to be a more reliable tool is that eye-tracking requires stable head and eye position in order to achieve accurate data. This could be difficult for patients with impaired physical or psychological conditions, even when using the chinrest. This means that some data could get lost or is inaccurate, so the practitioner should take this into consideration when interpreting the results. Nevertheless, eye-tracking has shown great potential in diagnosing dementia in an earlier stage, and as the algorithms used develop further, for example through more advanced machine learning techniques, the possibilities of diagnosing dementia earlier could become a reality.

The results of this study also have implications for the field of Artificial Intelligence. They have once more shown the vast potential of Artificial Intelligence in healthcare, as eye-tracking has shown to be a valuable tool in order to diagnose dementia or MCI earlier. Eye-tracking based tests could also inspire others to develop other AI techniques that could be used to assist neuropsychological evaluation further. More studies using AI to achieve a better or earlier diagnosis of dementia have already been done, such as an algorithm that is based on deep learning to accurately predict the risk of developing Alzheimer's disease as well as diagnose this impairment (Qiu et al., 2020). Another example of the potential that AI has in bettering dementia diagnostics is a research from Columbia University where machine learning models based on driving behavior were developed that are able detect early and mild cognitive impairment in older drivers with 88 percent accuracy (Di et al., 2021). These are just two examples of how Artificial Intelligence can be used outside of eye-tracking to revolutionize the healthcare industry. As Artificial Intelligence progresses at an extraordinary rate, it is interesting to consider the techniques that have yet to be invented or optimized. It is irrefutable that using AI as a tool to revolutionize the way dementia or other neurodegenerative disorders are diagnosed has just begun, and as more research comes out about the possibilities of AI, the more it will inspire future research on different methods. Future research on this topic could thus involve the development of different algorithms or techniques using Artifical Intelligence, such as developing or improving machine learning techniques, to improve eye-tracking algorithms. In addition, more research about objective oculometric biomarkers and their use for diagnosing dementia could be done to possibly improve the reliability or sensitivity of eye-tracking.

6

Conclusion

In this literary study I gave an overview of the possible ways in which eye-tracking can help diagnose dementia in a clinical setting to make the current diagnosing practices more reliable or sensitive. I asked the question 'To what degree can eye-tracking practices be of additional value in diagnosing dementia?'.

6.1. Sensitivity

I first looked at a way to use eye-tracking to diagnose dementia in an earlier stage. Different longitudinal studies agreed on the notion that there exists a relationship between MCI and the earlier stages of dementia. The studies did however disagree on the percentage of MCI patients that progress to dementia, as some concluded a progression rate of approximately 10 percent while other studies concluded that this progression rate was around 33 percent. These large differences could be due to variations in the sources of the subjects or cognitive testing between studies. However, even though these differences did exist between the studies, they all concluded that there was a relationship between MCI and dementia, which denotes that it could be useful to cognitively monitor MCI patients when attempting to diagnose dementia in an earlier stage. Studies also found that individuals with aMCI, one of the subtypes of MCI, have an even higher risk of developing dementia, making cognitive monitoring in this population possibly even more important. In order to thus determine the use of eye-tracking to diagnose dementia in an earlier stage I looked at the possibility of using eye-tracking to both diagnose dementia and MCI. Studies have shown that eye-tracking is a suitable method when used with the VPC task or AST to diagnose both impairments, as eye-tracking can be used to measure memory function, which is impaired in both MCI and dementia patients, as well as measure eye movement deficits using oculometrics, which develop early in dementia, even before cognitive deterioration becomes visible. This shows that eye-tracking is a very suitable technique when used in combination with these tasks to increase the sensitivity of the dementia diagnosis. Another benefit of using eye-tracking when attempting to diagnose dementia in an earlier stage is that using oculometrics as a biomarker is inexpensive and noninvasive when compared to alternatives. Furthermore, research has already shown that eye-tracking can be used for the rapid assessment of MCI or dementia, needing less than 3 minutes to diagnose a patients with adequate reliability, which is substantially less than the 10 to 20 minutes each neuropsychological test takes. All these different factors together show that eye-tracking can be a useful tool to make the process of diagnosing dementia more sensitive, thus making eye-tracking a valuable method.

6.2. Reliability

I next looked at studies regarding the ability to make diagnosing dementia more reliable. There appear to be advantages of using eye-tracking, specifically for highly educated individuals or those suffering from difficulties with motor or verbal responses. But this population is very specific and is the minority of the total population of individuals suffering from dementia that requires a diagnosis. An advantage of eye-tracking is that it uses objective biomarkers, such as oculometrics, and does not rely on the examiner as much as neuropsychological evaluation does, making it a more objective alternative to

diagnose dementia. However, eye-tracking does rely on calibration and poor calibration can result in inaccurate results, as can other technical deficiencies in the device. Besides, examiners are not excluded completely from the process: they still explain the exercises and results to the patient, making the process not fully objective as there exists room for human error. Overall, I do not believe that the conclusion can be drawn that eye-tracking makes a dementia diagnosis for the general patient more reliable, as there is insufficient evidence to make this conclusion.

6.3. Recommendation

I think that the VPC task or AST in combination with eye-tracking could be beneficial additions to current neuropsychological evaluation practices. I have a number of reasons to make the recommendation to incorporate these tests in standard neuropsychological evaluation.

The first reason is that it could help make the tracking of dementia possible even later in the impairment when patients might have difficulty giving motor or verbal responses. The VPC task or AST do not require motor or verbal responses en thus could provide a useful addition to standard neuropsychological evaluation in these individuals. The same would be the case for individuals suffering from subjective cognitive decline that did not feel like regular neuropsychological evaluation gave them accurate results, such as high educated elders. In these special cases incorporating eye-tracking by using for example the AST could prove useful as it can measure oculometrics as a biomarker. The AST results would thus still show signs of dementia, even if other neuropsychological evaluation tests are unable to detect the cognitive decline.

This brings me to my second reason why I make this recommendation: oculometrics are affected first in patients with dementia, even before cognitive functions are. Oculometrics are thus a great biomarker for the early diagnosis of dementia, which makes eye-tracking a useful tool as it can measure this biomarker well.

The last reason why I recommend the use of the VPC task or AST as an addition to neuropsychological evaluation is that eye-tracking could be a good tool to use in the cases where neuropsychological evaluation is too time consuming to be used in routine clinical practice. Eye-tracking has shown great potential in making an adequately reliable diagnosis of dementia, as well as in tracking the course of the disease in a patient. This could thus be a great solution for patients wanting or needing their impairment tracked regularly or those unable or unwilling to go through hours of testing.

Altogether the conclusion can be drawn that eye-tracking is a useful method when diagnosing dementia. It can make the diagnosing process more sensitive, making it a valuable technique to diagnose dementia earlier. It is however unsure whether eye-tracking can make diagnosing dementia more reliable, as there has been done insufficient research about this topic. There are specific cases in which eye-tracking could make the diagnosis more reliable, such as when a patient has difficulty giving motor or verbal responses, but this does not mean that the reliability of a dementia diagnosis using eye-tracking is in general higher than it would be using neuropsychological evaluation. It is thus unwise to exclusively use eye-tracking at this stage, but incorporating the VPC task or AST using eye-tracking in standard neuropsychological evaluation could be beneficial.

Bibliography

Alzheimer's Association. (n.d.). *Mixed dementia*. https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/mixed-dementia#:%7E:text=About%20mixed%20dementia,often%20coexist%20with%20Lewy%20bodies.

Alzheimer's Society. (n.d.). *Dementia symptoms and areas of the brain*. https://www.alzheimers.org.uk/about-dementia/symptoms-and-diagnosis/how-dementia-progresses/symptoms-brain

Bahia, V., & Viana, R. (2009). Accuracy of neuropsychological tests and the neuropsychiatric inventory in differential diagnosis between frontotemporal dementia and alzheimer's disease. *Dementia Neuropsychologia*, *3*(4), 332–336. https://doi.org/10.1590/s1980-57642009dn30400012

Bruscoli, M., & Lovestone, S. (2004). Is mci really just early dementia? a systematic review of conversion studies. *International Psychogeriatrics*, *16*(2), 129–140. https://doi.org/10.1017/s1041610204000092

Bueno, A., Sato, J., & Hornberger, M. (2019). Eye tracking – the overlooked method to measure cognition in neurodegeneration? *Neuropsychologia*, *133*, 107191. https://doi.org/10.1016/j.neuropsychologia.2019.107191

Carvalho, N. ., Noiret, N. ., Vandel, P. ., Monnin, J. ., Chopard, G. ., & Laurent, E. . (2014). Saccadic eye movements in depressed elderly patients (J. . Kassubek, Ed.). *PLoS ONE*, *9*(8), e105355. https://doi.org/10.1371/journal.pone.0105355

Chehrehnegar, N. ., Shati, M. ., Esmaeili, M. ., & Foroughan, M. . (2021). Executive function deficits in mild cognitive impairment: Evidence from saccade tasks. *Aging Mental Health*, 1–9. https://doi.org/10.1080/13607863.2021.1913471

Crawford, Taylor, S. ., Mardanbegi, D. ., Polden, M. ., Wilcockson, T. W., Killick, R. ., Sawyer, P. ., Gellersen, H. ., & Leroi, I. . (2019). The effects of previous error and success in alzheimer's disease and mild cognitive impairment. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-56625-2

Crawford, T., Higham, S., Renvoize, T., Patel, J., Dale, M., Suriya, A., & Tetley, S. (2005). Inhibitory control of saccadic eye movements and cognitive impairment in alzheimer's disease. *Biological Psychiatry*, *57*(9), 1052–1060. https://doi.org/10.1016/j.biopsych.2005.01.017

Crutcher, M., Calhoun-Haney, R., Manzanares, C., Lah, J., Levey, A., & Zola, S. (2009). Eye tracking during a visual paired comparison task as a predictor of early dementia. *American Journal of Alzheimer's Disease Other Dementiasr*, *24*(3), 258–266. https://doi.org/10.1177/1533317509332093

Csukly, G., Sirály, E., Fodor, Z., Horváth, A., Salacz, P., Hidasi, Z., Csibri, V., Rudas, G., & Szabó, D. (2016). The differentiation of amnestic type mci from the non-amnestic types by structural mri. *Frontiers in Aging Neuroscience*, *8*. https://doi.org/10.3389/fnagi.2016.00052

DeCarli, C., Mungas, D., Harvey, D., Reed, B., Weiner, M., Chui, H., & Jagust, W. (2004). Memory impairment, but not cerebrovascular disease, predicts progression of mci to dementia. *Neurology*, *63*(2), 220–227. https://doi.org/10.1212/01.wnl.0000130531.90205.ef

Di, X., Shi, R., DiGuiseppi, C., Eby, D., Hill, L., Mielenz, T., Molnar, L., Strogatz, D., Andrews, H., Goldberg, T., Lang, B., Kim, M., & Li, G. (2021). Using naturalistic driving data to predict mild cognitive impairment and dementia: Preliminary findings from the longitudinal research on aging drivers (longroad) study. *Geriatrics*, *6*(2), 45. https://doi.org/10.3390/geriatrics6020045

DSM-5. (2017). *Diagnostic and statistical manual of mental disorders* (5th ed.). Macmillan Publishers. https://doi.org/10.1176/appi.books.9780890425596.dsm17

Elkana, O., Eisikovits, O., Oren, N., Betzale, V., Giladi, N., & Ash, E. (2015). Sensitivity of neuropsychological tests to identify cognitive decline in highly educated elderly individuals: 12 months follow up (I. Gozes, Ed.). *Journal of Alzheimer's Disease*, *49*(3), 607–616. https://doi.org/10.3233/jad-150562

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., Krampla, W., & Tragl, K. (2007). Conversion from subtypes of mild cognitive impairment to alzheimer dementia. *Neurology*, *68*(4), 288–291. https://doi.org/10.1212/01.wnl.0000252358.03285.9d

Gauthier, S., & Touchon, J. (2005). Mild cognitive impairment is not a clinical entity and should not be treated. *Archives of Neurology*, *62*(7), 1164. https://doi.org/10.1001/archneur.62.7.1164

Gills, J. L., Bott, N. T., Madero, E. N., Glenn, J. M., & Gray, M. . (2020). A short digital eye-tracking assessment predicts cognitive status among adults. *GeroScience*, *43*(1), 297–308. https://doi.org/10.1007/s11357-020-00254-5

Haaksma, M. L., Calderón-Larrañaga, A. ., Olde Rikkert, M. G., Melis, R. J., & Leoutsakos, J. M. S. (2018). Cognitive and functional progression in alzheimer disease: A prediction model of latent classes. *International Journal of Geriatric Psychiatry*, *33*(8), 1057–1064. https://doi.org/10.1002/gps.4893

Klaib, A. F., Alsrehin, N. O., Melhem, W. Y., Bashtawi, H. O., & Magableh, A. A. (2021). Eye tracking algorithms, techniques, tools, and applications with an emphasis on machine learning and internet of things technologies. *Expert Systems with Applications*, *166*, 114037. https://doi.org/10.1016/j.eswa.2020.114037

Larrabee, G. J. (1992). Interpretive strategies for evaluation of neuropsychological data in legal settings. *Forensic Reports*, *5*(3), 257–264.

Li, Y., Xu, Y., Xia, M., Zhang, T., Wang, J., Liu, X., He, Y., & Wang, J. (2016). Eye movement indices in the study of depressive disorder. *Shanghai Arch Psychiatry*, *28*(6), 326–334. https://doi.org/10.11919/j.issn.1002-0829.216078

Liu, X., Faes, L., Kale, A., Wagner, S., Fu, D., Bruynseels, A., Mahendiran, T., Moraes, G., Shamdas, M., Kern, C., Ledsam, J., Schmid, M., Balaskas, K., Topol, E., Bachmann, L., Keane, P., & Denniston, A. (2019). A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: A systematic review and meta-analysis. *The Lancet Digital Health*, *1*(6), 271–297. https://doi.org/10.1016/s2589-7500(19)30123-2

Marandi, R., & Gazerani, P. (2019). Aging and eye tracking: In the quest for objective biomarkers. *Future Neurology*, *14*(4), FNL33. https://doi.org/10.2217/fnl-2019-0012

Mayo Clinic. (2019, April 26). *Lewy body dementia - symptoms and causes*. https://www.mayoclinic.org/diseases-conditions/lewy-body-dementia/symptoms-causes/syc-20352025

Mayo Clinic. (2021, January 8). *Frontotemporal dementia - symptoms and causes*. https://www.mayoclinic.org/diseases-conditions/frontotemporal-dementia/symptoms-causes/syc-20354737

Mitnitski, A., Graham, J., Mogilner, A., & Rockwood, K. (1999). The rate of decline in function in alzheimer's disease and other dementias. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *54*(2), M65–M69. https://doi.org/10.1093/gerona/54.2.m65

Munoz, D. P., & Everling, S. . (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience*, *5*(3), 218–228. https://doi.org/10.1038/nrn1345

National Institute on Aging. (n.d.). *What is lewy body dementia?* https://www.nia.nih.gov/health/what-lewy-body-dementia

Nyström, M. ., & Holmqvist, K. . (2010). An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data. *Behavior Research Methods*, *42*(1), 188–204. https://doi.org/10.3758/brm.42.1.188

Oyama, A., Takeda, S., Ito, Y., Nakajima, T., Takami, Y., Takeya, Y., Yamamoto, K., Sugimoto, K., Shimizu, H., Shimamura, M., Katayama, T., Rakugi, H., & Morishita, R. (2019). Novel method for rapid assessment of cognitive impairment using high-performance eye-tracking technology. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-49275-x

Petersen, R., Stevens, J., Ganguli, M., Tangalos, E., Cummings, J., & DeKosky, S. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review): Report of the quality standards subcommittee of the american academy of neurology. *Neurology*, *56*(9), 1133–1142. https://doi.org/10.1212/wnl.56.9.1133

Pinkhardt, E., Jürgens, R., Lulé, D., Heimrath, J., Ludolph, A., Becker, W., & Kassubek, J. (2012). Eye movement impairments in parkinson's disease: Possible role of extradopaminergic mechanisms. *BMC Neurology*, *12*(1). https://doi.org/10.1186/1471-2377-12-5

Qiu, S., Joshi, P., Miller, M., Xue, C., Zhou, X., Karjadi, C., Chang, G., Joshi, A., Dwyer, B., Zhu, S., Kaku, M., Zhou, Y., Alderazi, Y., Swaminathan, A., Kedar, S., Saint-Hilaire, M., Auerbach, S., Yuan, J., Sartor, E., … Kolachalama, V. (2020). Development and validation of an interpretable deep learning framework for alzheimer's disease classification. *Brain*, *143*(6), 1920–1933. https://doi.org/10.1093/brain/awaa137

Scinto, L., Daffner, K., Castro, L., Weintraub, S., Vavrik, M., & Mesulam, M. (1994). Impairment of spatially directed attention in patients with probable alzheimer's disease as measured by eye movements. *Archives of Neurology*, *51*(7), 682–688. https://doi.org/10.1001/archneur.1994.00540190062016

Staat van Volksgezondheid en Zorg. (2018). *Een samenhangend beeld van dementie en dementiezorg: Kerncijfers, behoeften, zorgaanbod en impact*. https://www.nivel.nl/sites/default/files/bestanden/Thema_rapportage_dementie_beveiligd.pdf

Whitehead, J., Li, L., McQuiggan, D., Gambino, S., Binns, M., & Ryan, J. (2018). Portable eyetracking-based assessment of memory decline. *Journal of Clinical and Experimental Neuropsychology*, *40*(9), 904–916. https://doi.org/10.1080/13803395.2018.1444737

Wilcockson, T., Mardanbegi, D., Xia, B., Taylor, S., Sawyer, P., Gellersen, H., Leroi, I., Killick, R., & Crawford, T. (2019). Abnormalities of saccadic eye movements in dementia due to alzheimer's disease and mild cognitive impairment. *Aging*, *11*(15), 5389–5398. https://doi.org/10.18632/aging.102118

World Health Organization. (2020, September 21). *Dementia*. https://www.who.int/news-room/fact-sheets/detail/dementia

Yaffe, K., Petersen, R., Lindquist, K., Kramer, J., & Miller, B. (2006). Subtype of mild cognitive impairment and progression to dementia and death. *Dementia and Geriatric Cognitive Disorders*, *22*(4), 312–319. https://doi.org/10.1159/000095427