Does sight provide insight into Alzheimer's dementia?

Katarina Marjanovič[1,2*]
Matej Perovnik[1,3*]
katarina.marjanovic@kclj.si
matej.perovnik@kclj.si
[1]Department of Neurology, University Medical Centre, Ljubljana
[2]Faculty of Education, University Of Ljubljana
[3]Faculty of Medicine, University Of Ljubljana
Ljubljana, Slovenia

ABSTRACT

Alzheimer's dementia (AD) is the most common neurodegenerative dementia. Its timely and early diagnosis is of great importance, as it allows patients to plan ahead and improve life quality with different non-pharmacological approaches. Several biomarkers, which allow for such a diagnosis, are already part of everyday clinical routine. While their role in the patient's assessment is undoubtedly valuable, they bear certain limitations, such as invasiveness and price. A search for a novel, non-invansive and inexpensive biomarker is underway. Eye movements have recently been proposed as a promising candidate for such a biomarker. Here, we offer a brief overview of both: the biomarkers most typically used in the clinical setting, and the eye movements, as tracked via eye tracker—a method, which already has a long tradition in the field of cognitive science.

KEYWORDS

Alzheimer's dementia, early diagnosis, biomarkers, eye movements, eye tracking, structural MRI, lumbar puncture, FDG PET

1 INTRODUCTION

Dementia is a clinical syndrome that involves impairment in at least two cognitive domains (i.e. memory, attention, executive functions, visuospatial abilities or language) and interferes with individual's ability to function in their daily activities [1]. It can arise as a consequence of various pathophysiological processes in the brain that start decades before the appearance of the first cognitive symptoms. The most common cause of dementia is Alzheimer's disease that causes 60 to 80% of all dementias [2]. Alzheimer's dementia (AD) is a final stage of Alzheimer's disease whose pathological hallmark is accumulation of misfolded proteins: amyloid β (Aβ) and Tau protein in the brain, which in turn cause synaptic dysfunction and neurodegeneration [3]. AD is usually preceded by symptomatic pre-dementia stage termed mild cognitive impairment (MCI), in which the physician can observe cognitive impairment that does not interfere with individuals' functional abilities [4].

There is a common public misconception that early diagnosis of AD is not essential due to the current lack of a disease-modifying drug. But such diagnosis is of paramount importance. Firstly, it allows people with dementia and their caregivers to plan ahead and thus ameliorate caregiver burden. Furthermore, certain non-pharmacological interventions are more effective in the earliest stages of AD and early diagnosis can lead to early involvement into drug trials [5]. Additionally, bearing in mind that about 5–10% of patients with MCI progresses to dementia per year [6], we can also highlight the importance of accurate diagnosis of Alzheimer's disease and accurate identification of MCI patients who will progress to AD.

2 DIAGNOSIS OF DEMENTIA

Diagnosis of dementia is inherently linked to firstly, ruling out potentially treatable causes and secondly, diagnosing the underlying neurodegenerative process. In this section, we will first briefly address other, potentially treatable causes of cognitive impairment and then present the biomarkers of the most common neurodegenerative cause of dementia—Alzheimer's disease.

Individuals with cognitive impairment firstly undergo blood screening for systemic abnormalities (vitamin B_{12}, folate, thyroid-stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function) and structural imaging with magnetic resonance imaging (MRI) or at least computer tomography (CT) to exclude other causes of dementia (i.e., tumor, abscess, stroke or normal pressure hydrocephalus) [7]. Core diagnostic criteria for AD are still rooted in clinical presentation, meaning that the physician can make an AD diagnosis even without the use of biomarker information [1]. Because clinical diagnosis of AD is not in concordance with pathological diagnosis in around 30% of cases [8], there has been a shift towards promotion of biomarker-supported diagnosis in recent years [9]. Biomarker is a characteristic that can be measured objectively and reflects a certain biological or pathological process [10]. Various biomarkers are already a part of everyday clinical routine.

Structural MRI is a recommended and widely used imaging method that can be used to assess atrophy in medial and lateral temporal lobe, medial parietal cortices and hippocampi—structures that are affected early and disproportionally in AD. Atrophy reflects the loss of neurons and can be seen clearly as disease progresses, but patterns of atrophy often overlap between different dementia syndromes and changes can be very subtle in early stages. Furthermore, structural MRI is useful for the assessment of the vascular burden—an important co-morbidity in AD [11]. Two other commonly used biomarkers of AD are analysis of cerebrospinal fluid (CSF) and functional brain imaging with 2-[^{18}F]Fluoro-2-deoxy-D-glucose and positron emission tomography (FDG PET). Lumbar puncture is performed to obtain CSF from which concentrations of Aβ_{42}, phosphorylated Tau and total Tau proteins can be measured. Reduction in concentration of Aβ_{42} protein (due to increase in extracellular binding in the brain)

*Both authors contributed equally to this review.

Information society '20, October 5–9, 2020, Ljubljana, Slovenia

in CSF can be observed decades before appearance of first cognitive symptoms, but Aβ_{42} concentration reaches plateau already in the pre-symptomatic disease stage [12] and is thus not a suitable biomarker of disease progression. Furthermore, lumbar puncture is an invasive procedure with a non-negligible percentage of mild complications such as back pain or headache, however the percentage of serious complications is very low (< 1%) in specialized institutions [13]. FDG PET is a non-invasive brain imaging modality that provides information about synaptic dysfunction, which precedes atrophy, and is commonly used in early detection and differential diagnosis of dementia. Furthermore, it also provides an important insight into disease progression [14]. Because FDG PET imaging involves radiation exposure, it is not recommended to be performed more than once per year. Additionally, FDG PET is a relatively expensive procedure [11].

In summary, while the current biomarkers are able to detect AD in the earliest stages, they are either invasive (e.g., lumbar puncture) or relatively expensive (e.g., MRI, FDG PET). A discovery of a reliable, noninvasive and inexpensive biomarker would thus greatly advance the availability of early diagnosis of AD [15]. The search for such an alternative biomarker has already begun, and the research of the past two decades has yielded important advancements. In the next paragraphs we offer a short overview of one such potential biomarker—eye movements, as tracked via eye tracker. In order to do so, we first need to shift our focus away from the most commonly defined features of AD.

3 VISON IMPAIRMENTS IN ALZHEIMER'S DEMENTIA

As reflected in the clinical diagnostic criteria for AD, described above, the primarily addressed disorders of AD are the disorders of cognitive functioning [1]. However, a common, yet largely ignored feature of AD are also alterations in sensory capacity, particularly in visual processing [16, 17]. These are of extreme importance especially when talking about timely diagnosis of the AD, since they are present already in the early stages of the symptomatic disease [16, 17]. Possibly, these changes are often overlooked due to the fact that they are not present in all types of visual processing. For example, visual acuity, which is most commonly tested when an individual initially complains that their vision is not quite right, is typically no more impaired than in healthy elderly individuals [16]. But additional deficits can be observed in other, more subtle types of visual processing, such as contrast sensitivity (i.e., the ability to distinguish gratings of varying spatial frequencies at different contrast levels) [16], color discrimination (i.e., ability to distinguish different shades of colors) [18, 19], and eye movements [19, 20].

Despite the fact that these deficits are traditionally still not dealt with in clinical environment [21], the last two decades of interdisciplinary research have brought to light numerous new findings, particularly about the eye movement alterations in AD. This field of studies has recently been gaining more and more attention, and has since largely progressed along two lines of research: while the first one deals with correlation of the eye movement alterations and the disease severity, the second one focuses on the applicability of the eye movement alterations for early detection of cognitive decline [e.g., 19, 20]. In the remainder of this abstract, we will address the latter in more detail, and explore the potential of the eye movements as possible biomarker for diagnosis of AD.

3.1 Eye movements and their alterations in AD

Unlike the other methods, described above, eye movements, as tracked and recorded via eye tracker, present a sensitive, non-invasive, and inexpensive method [22, 23, 15], which allows for testing in a simple and everyday-like setup. As such, eye tracking presents an ideal method for testing patients with cognitive decline, since the tasks they perform during testing are relatively natural and thus easily comprehensible, without complicated instructions. Additionally, the method is appealing to the patients also due to the fact that they are simply sitting comfortably in front of a computer screen, while their head is typically stabilized through a chin rest, allowing them to relax their posture without compromising the accuracy of the recording.

In healthy individuals, who are not experiencing any kind of processing difficulties, the typical oculomotor behavior can be described with a series of eye movement measures. Here, we offer a description of two of them as an example. When we, for example, look at a presented picture, search for an object or read a text in font of us, we continuously make rapid linear eye movements—so called saccades, which can reach velocities as high as 500° per second [24]. During a saccade, the sensitivity to visual input is reduced, thus we essentially do not obtain new information from our environment while our eyes are moving [25]. In order to obtain this information, we make a series of stops in between the saccades—so called fixations, which typically last about 250ms [25, 20]. During this time our eyes remain relatively still, focusing on the information that is available in the momentary foveal vision (i.e., the center of the visual field, with the highest visual acuity) [26]. The role of the saccades is thus to move our eyes onto a new region of the processed stimuli, where we make a fixation to bring new informaton into our foveal vision, and consequently into our attention.

The main reason why eye tracking can so readily be used for an early detection of the neurodegenerative alterations is that it allows for a simple investigation of complex viewing behavior that humans automatically engage in when they are driven by top-down, goal-directed processes. Given the intimate link between the eye movements and cognition, any alterations in the typical oculomotor behavior can thus be used to infer AD-related changes in cognitive processing [27]. Carefully selected tasks that trigger complex viewing behavior, in which attention and its allocation, inhibitory control, working memory, or decision-making are required to successfully accomplish a goal, thus present an ideal testbed for early detection of the AD, since all these processes are altered already in the early stages of AD [20]. Importantly, such tasks are already well-defined and well-explored in the frame of studies with healthy participants in the filed of cognitive science. Here, we offer a short overview of the patient's performance in three such tasks: visual search, natural reading and antisaccade task.

3.1.1 Visual search task. In essence, visual search task is goal-directed search for a target (e.g., a specific object) among a number of distractors in an environment [27]. Compared to healthy control participants, patients with AD exhibit delayed target detection [27, 20], longer fixation durations [20, 28] and longer and less systematic exploration [29, 30, 28], which is often described as stochastic [29].

3.1.2 Natural reading task. Despite the fact that reading is an activity in which (literate) humans engage in on an everyday

basis and without much effort, this is a very demanding cognitive task [31, 32, 33, 34]. Successful reading process demands not only simultaneous processing of different linguistic information (e.g., letter identification, morphologic and semantic processing), but also precise coordination, attention allocation and planning (e.g., where and when will the eyes move in the text) [33]. Compared to healthy control participants, patients with AD exhibit a reading pattern that noticeably differs from a typical one, and is similar to alterations described in visual search task: longer fixation durations, increased occurrence of several fixations on the same word (so called refixations), increased number of saccades, which are shorter than the typical span of 8-9 characters [30, 20]. Additionally, there is also an increase of word skips (i.e., number of times a word is not directly fixated) during the first reading, which is accompanied with a larger number of regressions back to the already read parts of the text [26, 20, 30].

3.1.3 Antisaccade task. In a typical anti-saccade task the participants are required to inhibit a reflexive saccadic eye movement towards a presented target. Usually, their eyes are fixated on the central point on the screen until the so called distractor target appears in the peripheral visual field, either left or right of the fixation point. At this timepoint, participants are required to make a saccade to the opposite direction of the screen. Failure to do so results in so called anticcade error. Compared to healthy control participants, patients with AD exhibit an increase in the antisaccade errors [35, 36], as well as also a decrease in the number of corrected errors [36]. A very recent study reveals that such eye movement alterations are already present in patients with MCI. Importantly, these alterations reliably differ between the patients with amnestic and non-amnestic MCI, where the former are at a much greater risk of progressing to AD [15].

4 CONCLUSION

In the recent years, AD research and clinical work is experiencing a shift towards early and biomarker-oriented diagnosis. We are now increasingly more aware of the importance of early detection of the disease, which would significantly contribute to ameliorating the disease burden, while timely and accurate diagnosis could also accelerate the research of disease-modifying drugs. As addressed in this review, several biomarkers which allow for such a timely diagnosis are already available and are an important part of clinical diagnostic. Recently however, a need for a non-invasive and inexpensive biomarker has been emphasized. Eye movements, as tracked via eye tracker, have been proposed as a promising candidate for such a biomarker, since a rapidly growing number of studies in the recent years have demonstrated that they offer a highly reliable and sensitive method for detection of impairment of cognitive control in AD. Importantly, studies demonstrate that the eye movement alterations can, at least in certain tasks, already be observed at the early stages of the AD and even in patients with MCI. Even more importantly, the recent findings indicate that they can also reliably distinguish between the patients with MCI who are at risk of progressing to AD, and those who are more likely to progress to other disorders.

But the gap between the interdisciplinary research and the application of this method to everyday clinical practice still looms large. In the future work, the eye movements should be studied in more detail in a variety of tasks and in patients in different disease stages. Furthermore, prospective longitudinal eye movement studies could offer us an insight into disease progression. This could lead to a development of a sensitive battery of simple tasks, tailored to detecting and monitoring the disease at its specific stages, and to the specific needs of the patients with dementia, who require natural and simple tasks, which do no trigger any discomfort or risk of misunderstanding the task instructions.

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