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Survey Paper

On the early diagnosis of Alzheimer's Disease from multimodal signals: A survey

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ABSTRACT

Introduction: The number of Alzheimer's Disease (AD) patients is increasing with increased life expectancy and 115.4 million people are expected to be affected in 2050. Unfortunately, AD is commonly diagnosed too late, when irreversible damages have been caused in the patient.
Objective: An automatic, continuous and unobtrusive early AD detection method would be required to improve patients' life quality and avoid big healthcare costs. Thus, the objective of this survey is to review the multimodal signals that could be used in the development of such a system, emphasizing on the accuracy that they have shown up to date for AD detection. Some useful tools and specific issues towards this goal will also have to be reviewed.
Methods: An extensive literature review was performed following a specific search strategy, inclusion criteria, data extraction and quality assessment in the Inspec, Compendex and PubMed databases.
Results: This work reviews the extensive list of psychological, physiological, behavioural and cognitive measurements that could be used for AD detection. The most promising measurements seem to be magnetic resonance imaging (MRI) for AD vs control (CTL) discrimination with an 98.95% accuracy, while electroencephalogram (EEG) shows the best results for mild cognitive impairment (MCI) vs CTL (97.88%) and MCI vs AD distinction (94.05%). Available physiological and behavioural AD datasets are listed, as well as medical imaging analysis steps and neuroimaging processing toolboxes. Some issues such as "label noise" and multi-site data are discussed.
Conclusions: The development of an unobtrusive and transparent AD detection system should be based on a multimodal system in order to take full advantage of all kinds of symptoms, detect even the smallest changes and combine them, so as to detect AD as early as possible. Such a multimodal system might probably be based on physiological monitoring of MRI or EEG, as well as behavioural measurements like the ones proposed along the article. The mentioned AD datasets and image processing toolboxes are available for their use towards this goal. Issues like "label noise" and multi-site neuroimaging incompatibilities may also have to be overcome, but methods for this purpose are already available.

1. Introduction

Peoples' life expectancy is growing continuously in the developed countries, making the population increasingly old. Even if this is a positive reality, it also brings unwanted consequences such as an increasing number of diseases, including the Alzheimer's Disease (AD). It is estimated that AD will double its frequency in the next 20 years [1] and that 115.4 million people will suffer from it in 2050 [2]. Furthermore, while deaths attributed to other health problems such as heart disease have decreased in the last years, deaths attributed to AD between 2000 and 2010 have increased in 68% [3]. Nowadays, it does not exist a cure for AD [4], neither a 100% reliable diagnosis until a post-mortem analysis is done. Only some symptomatic treatments that are effective for limited periods in subgroups of patients are available [5]. Life expectancy of the patients diagnosed with AD is currently less than 7 years [4].

Even if it is thought that AD is the result of a combination of genetic, environmental and lifestyle factors [6,7], the initiating events that make someone develop this type of dementia remain still unknown [8]. The most effective method of controlling AD's progression is believed to be based on an early diagnosis and a

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good management strategy started from the very beginning of the cognitive decline [9,10], but, nowadays, the diagnosis is mainly accomplished using psychological tests that become positive when the disease is practically irreversible [11].

This paper is structured as follows. In the remainder of this section, AD and its progress are explained (see Sections 1.1 and 1.2), and the need for an early diagnosis method is highlighted (Section 1.3). In Section 2 the methodology used to conduct the literature review is explained. In Section 3, the current state of cognitive, psychological, physiological and behavioural diagnostic methods and biomarkers is exposed and in Section 4, the reviewed state of the art is critically analysed highlighting the research gaps. In Section 5 some of the useful tools for the multimodal AD detection research are considered, namely, the publicly available datasets (Section 5.1), the standard methods for medical imaging analysis (Section 5.2) and the neuroimaging processing toolboxes (Section 5.3). In Section 6, some of the real-world datasets' issues are discussed. Finally, in Section 7, a conclusion is given along with clues for future work.

1.1. Definition

AD is a progressive, degenerative disorder that attacks brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioural changes [12]. It is a neurological disorder that mostly affects people over 65 years old and whose incidence rate grows exponentially with age [13]. It is the most common form of dementia [14] and unlike what some people may think, AD is not a normal part of ageing [15].

1.2. Phases

It is believed that people developing AD undergo three different stages [16]. The first one is the preclinical AD stage, where changes in the brain, in the blood and in the cerebrospinal fluid (CSF) may start happening, but the patient does not show any symptoms [3]. Therefore, nowadays, this phase cannot still be detected. In fact, it is believed that this stage can start 20 years before any symptom is evidenced. The Nun Study, one of the most significant longitudinal studies in the area of AD research, has even shown evidences of correlations between youth linguistic ability and late life progression to AD [17].

The second stage of the disease is called the mild cognitive impairment (MCI). In this stage, symptoms related to the thinking ability may start to be noticeable for the patients themselves and for the nearest family members, but they do not affect their daily life [3]. Not all the people diagnosed with MCI develop AD, but only an estimated 10–15% of them every year [18,19] and the reason why some people develop dementia and others do not, remains still unknown. When a patient is diagnosed with MCI, a specific diagnosis procedure must start to understand which disease or condition is responsible for the deficit [20]. Two different types of MCI are distinguished: amnesic MCI (aMCI) and non-amnesic MCI [9]. The former refers to patients who have impairment in the memory domain, and the latter to patients who have impairment in one or more non-memory domains of cognition, as, for example, attention or language processing. It is believed that subjects suffering from aMCI are more likely to develop AD [21].

The final stage of the disease is called dementia due to AD, where memory, thinking and behavioural symptoms are already evident and affect the patient's ability to function in daily life.

1.3. The need for an early diagnosis method

AD symptoms are occasionally recognized by the patients themselves, but in the vast majority of cases, the caregivers or the close familiars and friends are the ones who realize the behavioural and cognitive changes suffered by the AD patients. The severity of these symptoms is not always easy to notice. The problem is that AD symptoms are in many cases confused with a normal ageing process, and thus, doctors are not consulted until being too late, resulting in a late diagnosis [22]. In the survey carried out in [23], 64% of the caregivers affirmed that before the diagnosis, they considered the behaviour changes suffered from the patients as part of the normal ageing process. 67% of them agree that this made the diagnosis to be delayed. Furthermore, once in the hand of specialists, it is not yet easy to correctly diagnose AD. Even the most experienced specialists fail in about 10–15% of cases to correctly diagnose AD [24]. In fact, the definite diagnose can only be made by a post-mortem examination of the brain. Nowadays, a patient suspicious of suffering from AD can be clinically diagnosed with an accuracy of about 90%, drawing on medical records, physical and neurological examination, laboratory tests, neuroimaging and neuropsychological evaluation [25]. Most of these methods used for AD diagnosis are time-consuming and they require a clinician intervention [26], involving annoying displacements to hospitals, which can be specially difficult with elderly. Moreover, the monitoring of the progression of the disease is very costly [27] and, therefore, not well enough studied. Neuroimaging is being increasingly used because it offers to physicians the possibility to analyse the patients' brains while they are alive. Nevertheless, when changes can be appreciated with the naked eye, it is normally too late. That means that the brain has evident signs of atrophy, or that too many neurofibrillary tangles (NFT) and Amyloid plaque deposits can be found on it. Non-invasive, fast, inexpensive and reliable AD diagnosis methods are still to be developed [4].

An early diagnosis of the disorder can be extremely helpful for the patients because they can have access to treatments that can delay some symptoms, being much more effective in the early stages [4], as well as to programs and support services, when the disorder has no yet progressed too much [22]. Furthermore, this can allow them to take part in the decision of their future, as, for example, about their care and everyday life or about money and legal concerns. Early diagnosis can also help to improve AD survival rate [28].

Thereby, for an early diagnosis of AD it is necessary to be able to detect the most subtle symptoms of any type. Taking into account the multimodal nature of AD symptomatology, it is clear that the most efficient and reliable early AD detection methodology can not only rely on measurements of a unique domain, i.e. only physiological or behavioural symptoms, but on the combination of several modalities, that could allow to detect all the subtle changes of all domains from the very beginning and to contrast them with other type of symptoms for a reliable diagnosis. The multimodal nature of other disorders such as stress has also been analysed, and an approach for its early detection proposed [29], demonstrating the feasibility and application of these methods to multiple disorders.

Nevertheless, subtle changes are not easily noticeable. People, without the aid of technology, are not able to recognise the so small behavioural shifts that AD patients may undergo, not suspecting the problem until being too late. Technology that could make this process easier is highly required to speed up the whole process. Physicians may not be able to correctly diagnose AD if they do not find the necessary physiological traces for it. Automated computer aided diagnosis (CAD) techniques are needed to facilitate physician's diagnosis of complex diseases in individual patients [30]. Thus, technology that can help in the early detection of AD based on subtle behavioural and physiological changes must be developed.

Recently, a review of non-invasive innovative diagnostic tools for the early detection of AD has been published [31]. Nevertheless, this article did not emphasize on the multimodal nature of the disorder, neither in the automatic assessment of dementia based