Concept of developing an 'unbiased' AI to spot & predict Alzheimer's Disease 6 years earlier than Clinical diagnosis

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Abstract: According to the World Health Organization, it is estimated that 50 million people are diagnosed with dementia worldwide, exponentially increasing to 10 million each year**.** Out of that, 60-80% account for Alzheimer's Disease (AD) and it is also predicted that by 2050 number of individuals above the age of 60 will be doubled, leading to an increase in the number of AD Cases and burden on the entire healthcare system. Human brain activity happens through interaction between billions of neurons actively translating to generate thought, behaviour & cognitive functioning. Patients with AD go through Mild Cognitive Impairment (MCI) which can be spotted through neuroimaging techniques. Functional magnetic resonance imaging (fMRI) measures brain activity based on blood flow change, and calcium imaging detects the activity of neurons over time to differentiate the functioning of neural circuits. Applying the Multilayered clustering algorithm 'an unbiased AI' on brain imaging data and combining it with Brain-Computer Interface (BCI), it is possible to predict imaging recognition. This study critically analyses the concept of an 'unbiased' deep learning algorithm trained with Positron Emission Tomography (PET) images of the brain, which is tested to spot signs of Alzheimer's disease six years ahead of final clinical diagnosis. Without a certain amount of available data, it is a very tough and complex procedure to map brain activity, measure & model as neural activity is not linear and human behaviour is unpredictable but not random. In addition, training neural networks such as deep RNNs to accurately predict the patterns requires a significant amount of big imaging datasets.

Keywords: Alzheimer’s Disease prediction, Unbiased AI, Brain-Computer Interface

Introduction

Alzheimer's disease, vascular dementia, Lewy body, and frontotemporal dementia are the most prevalent underlying pathologies that cause dementia. Dementia is a clinical syndrome brought on by neurodegeneration, and it is characterised by an imperceptibly worsening of cognitive function and the ability to live independently. For many high-income countries, social and health care is a top priority. Recent developments include creating particular plans or strategies by the UK, France, Norway, the USA, and South Korean governments. Government solutions are being driven by population ageing, which significantly impacts the rise of the dementia crisis. Dementia mainly affects older people; among them, it is a significant cause of dependency, and young-onset instances are increasingly being recognised (Sousa et al., 2009 & Sousa et al., 2010). For China, India, and Latin America, the share of older people is expected to rise remarkably quickly (World Population Prospects, 2002). By 2050, there will be 1.25 billion more individuals over 60, or 22% of the world's population, with 79% residing in less developed areas. The preparation of the healthcare system and awareness of dementia is

substantially less developed in these areas. Therefore, in light of the rapidly growing demographic and health transitions, monitoring the global prevalence of this debilitating disorder and its regional distribution is crucial.

About 10 billion linked neurons make up the brain. In the neurological system, neurons are electrically excitable cells that process and send information. The dendritic tree of a neuron connects to a thousand nearby neurons. One of the dendrites on those neurons receives a positive or negative charge when one of those neurons fires. Via spatial and temporal summation procedures, the strengths of all received orders are combined. The soma is then given the combined input (cell body). Processing incoming and outgoing information does not significantly involve the soma or the enclosing nucleus. Their main job is to maintain the neuron function by performing ongoing maintenance. The axon's numerous divisions unalter the output strength; it keeps the same intensity at each terminal button.

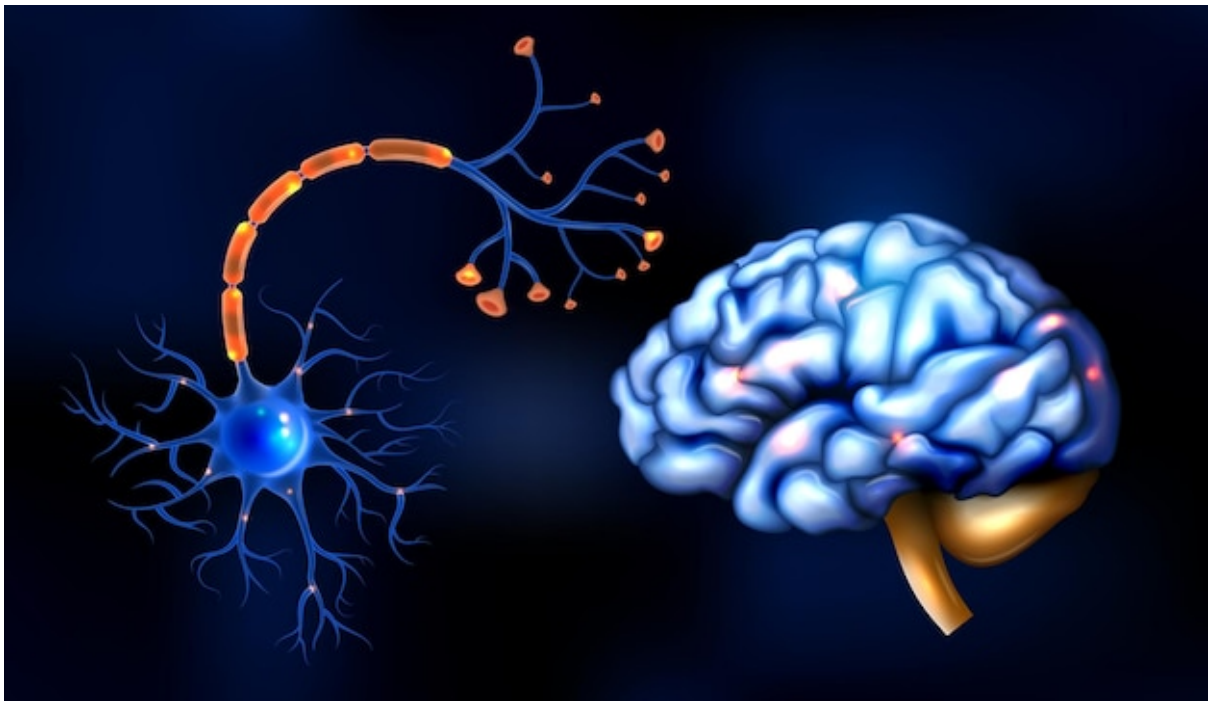
Each terminal button has a synapse, a tiny opening connecting it to neighbouring neurons. Each synapse's physical and neurochemical properties determine the intensity and polarity of the new input signal. The brain is the most adaptable and vulnerable in this area (Shi, 2021).

Alzheimer's disease (AD) is the most common cause of dementia among people aged 60 (Bischkopf et al., 2002). The prevalence of AD ranges from 6.44% in south India (Mathuranath et al., 2010) to 4.86% in Shanghai (Zhang et a., 1990) China to 3.92% in Sri Lanka for populations above 65 years (de Silva et al., 2003). The main clinical feature of AD is increasing memory impairment followed by impairment of other cognitive domains, a characteristic pathological cortical and hippocampal atrophy, the histological feature of senile plaques of amyloid deposits and neurofibrillary tangles consisting of intraneuronal tau fibrillary tangles (Humpel, 2011). The prevalence of AD is expected to increase dramatically as the global population ages. A better understanding of this dementing disease, therefore, is essential. Early diagnosis combined with a comprehensive management strategy initiated early in the course of the cognitive decline will likely be the most effective method of controlling the progression of AD (Wattamwar et al., 2010; Landau et al., 2010; Buckner et al., 2005). One of the significant handicaps towards achieving this is the difficulty in the early and definitive diagnosis of AD. Over the past decade, there has been a tremendous amount of research in the field of biomarkers of AD. In this article, we review the current knowledge of structural imaging changes associated with AD. Structural MRI and functional studies such as PET and SPECT are widely researched in diagnosing AD (Ortiz-Teran et al., 2011; Barber, 2010; Zhang, 2012). Structural and functional Imaging may be helpful in the early Diagnosis of AD (Ferreira et al., 2011 & Masdeua et al., 2005). With increasing research in disease-modifying therapy in AD and recognition of mild cognitive impairment (MCI) as a very nascent stage, early Diagnosis of AD will assist in the early initiation of disease-modifying therapy. This, in turn, will aid in improving the quality of life of patients with AD.

MCI is a predementia condition shown to have a high likelihood of progression to AD (Karas, 2004 & Burns, 2002). It is characterised by impairment in one domain of cognition with relatively preserved other cognitive parts in the presence of unimpaired functional abilities (Petersen, 2003 & Petersen et al., 1999). MCI can be categorised as amnestic MCI (aMCI) and non-amnestic MCI (naMCI). aMCI refers to patients who are functionally independent but with impairment in the memory domain. Whereas naMCI includes functionally independent patients with impairment in one or more non-memory domains of cognition such as attention, executive functioning, language and visuospatial processing etc. Some studies suggest that patients with the aMCI subtype have a higher risk of progression to AD (McEvoy et al., 2009).

Inside Human Brain

The Brain in Action



Pic courtesy: Freepik

Neurons

- The brain has billions of neurons, each with an axon and many dendrites.
- To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.

AD and Brain

Preclinical AD

- AD signs are first noticed in the entorhinal cortex, then proceed to the hippocampus.
- Affected regions begin to shrink as nerve cells die.
- Changes can begin 10-20 years before symptoms appear.
- Memory loss is the first sign of AD.

Mild to moderate AD

- AD spreads through the brain. The cerebral cortex begins to shrink as more and more neurons stop working and die.
- Mild AD signs can include memory loss, confusion, trouble handling money, poor judgement, mood changes, and increased anxiety.
- Moderate AD signs include increased memory loss and confusion, problems recognising people, difficulty with language and thoughts, restlessness, agitation, wandering, and repetitive statements.

Severe AD

- In severe AD, extreme shrinkage occurs in the brain. Patients are entirely dependent on others for care.
- Symptoms can include weight loss, seizures, skin infections, groaning, moaning, grunting, increased sleeping, and loss of bladder and bowel control.
- Death usually occurs from aspiration pneumonia or other infections. Caregivers can turn to a hospice for help and palliative care.

Warning Signs

- ✓ Memory loss that disrupts daily life
- ✓ Difficulty planning or solving problems
- ✓ Forgetting how to do familiar tasks
- ✓ Confusion with dates, times or place
- ✓ Withdrawal from work or social situations; difficulty initiating activities and participating in social interactions
- ✓ Misplacing objects and the inability to retrace steps
- ✓ The trouble with spatial relationships
- ✓ New problems with words in speaking or writing
- ✓ Mood swings and changes in personality
- ✓ Altered decision-making; poor judgement or relying on someone else, such as a spouse, to make decisions or answer questions

Importance of Early Diagnosis

Rules out the possibility of other treatable medical conditions that could cause dementia

Points out additional medical conditions that may exist

Allows for the opportunity to plan for the future

Opportunity to participate in clinical trials

Diagnosing AD

a detailed patient history

information from family and friends

physical and neurological exams and lab tests

neuropsychological tests

imaging tools such as CT scans or magnetic resonance imaging (MRI). PET scans are used primarily for research purposes

What is fMRI

BRAIN IMAGING METHOD for obtaining 3D images related to activity in the

brain.

fMRI measures the ratio of oxygenated haemoglobin to deoxygenated haemoglobin in the blood at various locations in the brain.

Performs brain activation studies by measuring BRAIN-OXYGEN-LEVEL DEPENDENT (BOLD) signal.

Difference between MRI and fMRI

MRI views anatomical structure

Studies water molecule's hydrogen nuclei

Views in high resolution of the difference between the tissue types concerning space

fMRI views metabolic function

fMRI calculates the level of oxygen

Views the tissue difference concerning the time

What is functional Imaging?

Measures Brain activity by measuring BOLD signals

BOLD signals and neural activation are dependent, and the signal distorts the magnetic field

Working of fMRI

The brain requires a steady supply of oxygen for metabolism.

The oxygen is provided by haemoglobin in the blood.

Neural activity consumes oxygen, so on activation, there is a momentary decrease in blood oxygenation

The blood flow increases to bring more oxygen to the activated area

The blood flow peaks after around 6 seconds

fMRI experiments procedure

- Alternate the subject's neural state between 2 (or more) conditions using sensory stimuli, tasks to perform,
- It can only measure relative signals, so it must look for *changes* in the signal between the conditions.
- Acquire MR images repeatedly during this process.
- Search for voxels whose NMR signal time series (up-and-down) matches the stimulus time series pattern (on and off)
- fMRI data analysis is pattern matching *in time*
- Signal changes due to neural activity are small

- Need 500 or so images in time series (in each slice) ➔ takes 30 min or so to get reliable activation maps
- Usually, break image acquisition into shorter "runs" to give the subject and scanner some break time
- Other minor effects can corrupt the results ➔ post-process the data to reduce these effects & *be vigilant*
- Lengthy computations for image recon and temporal pattern matching ➔ data analysis usually done offline

fMRI Data Collection

It consists of a time series of the 3D functional images of the subject's brain

The time interval between each image is called the **time of repetition (TR),** usually

between 2-3 sec.

Each 3D image consists of 20-30 slices of 2D image

One 2D slice contains 64 X 64 voxels

Physically each voxel corresponds to 2mm X 2mm X 2mm

fMRI Data Pre-processing

SLICE-TIME CORRECTION: Each voxel is acquired in one TR at different times. This causes a discrepancy between the actual hemodynamic response of a region of interest. The correction technique is a temporal interpolation.

HEAD MOTION CORRECTION: Employs motion correction algorithm

NORMALISATION: Involves multiple subjects. A standard brain atlas is developed. Available data from different subjects are correctly mapped to the atlas.

The Primary Objective

fMRI has emerged as a powerful technique to locate the human brain's activity

while engaged in a particular task or cognitive state.

We consider the inverse problem of detecting the cognitive state of a human subject based on the fMRI data.

We aim to identify the cognitive state of the human subject that is persistent with time, given the fMRI activity within that interval.

Popular classification techniques includeGaussian Naive Bayes, k-Nearest Neighbour and Support Vector Machines.

The Process

An fMRI scanner measures the value of the fMRI signal at all the points in a

three-dimensional grid or image every few seconds (4-6 seconds).

The number of voxels constituting the whole brain is huge (1,20,000 – 1,80,000), resulting in very high dimensional data.

Since the signals measure tiny fluctuations in the magnetic field, known as the

Blood Oxygen Level Dependent (BOLD) response, the signal-to-noise ratio (SNR) for fMRI data is deficient.

Hence fMRI data is very noisy.

The Classifier

The classifier is a function of the form:

f : fMRI-sequence(t1, t2) CognitiveState

Where fMRI-sequence(t1, t2) is the sequence of fMRI images collected during the contiguous time interval [t1, t2], and CognitiveState is the set of cognitive states to be discriminated.

Multi Voxel Pattern Analysis

Traditional fMRI response finds voxels that show statistically significant

responses. They average the voxels.

MVPA uses a pattern-classification algorithm appliedto multiple voxels to decode the pattern of brain activity.

It offers reduced noise and increased sensitivity.

Why fMRI?

Most people are familiar with the functional magnetic resonance imaging, or fMRI, method of capturing cerebral activity. The multicolour images of specific brain regions being lit up reflect blood flow in the brain rather than recording the activity of neurons. Even though it is indirect, fMRI enables scientists to infer patterns of neuronal activity. More specifically, the signal you see represents the relative presence of oxygenated vs deoxygenated blood; active regions require more oxygenated blood.

Modern neuroscience research relies heavily on fMRI because it makes it possible to correlate human brain function and architecture (as established by a structural, as opposed to a functional, MRI scan). There are certain limitations, however. A cubic millimetre contains about 60,000 neurons, which is enough to support the entire life of a fruit fly or lobster.

However, complex perceptual decisions only take hundreds of milliseconds, making the spatial (one mm3, relating to location) and temporal (1-2 sec, relating to time) resolutions subpar compared to what we would want. Nevertheless, fMRI does not provide users access to these data. However, fMRI offers a unique perspective on the location and degree of potential localisation of various functions within the human brain. For example, its spatial and temporal resolution is still being improved by making the approach sensitive to neuronal changes rather than blood flow changes. The ability of fMRI to "map" or identify the most likely location of cognitive function within the human brain is unmatched by any other method now in use. Thus, the ideal method for brain mapping and data retrieval is fMRI. To advance the development of data and analytics with testing algorithms, it is essential to distinguish between oxygenated and deoxygenated blood regions clearly, indirect neuron patterns, and not just those that follow broader aspects like localised structural mapping, sensitivity to neural changes, and blood flow.

Related Earlier Works

In a recent study published in Radiology, researchers used machine learning and neuroimaging to determine if a patient will eventually acquire Alzheimer's disease when they initially displayed memory loss (Ding et al., 2019).

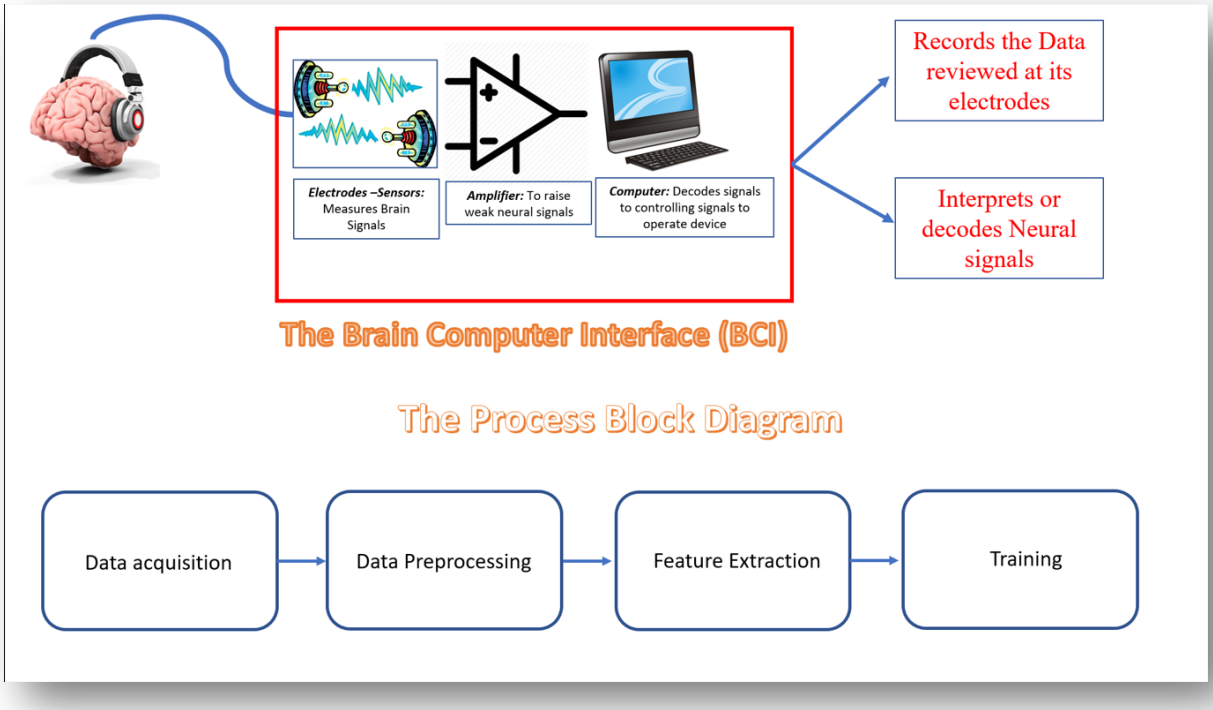
Researchers have mainly looked into the possibility of using PET scans, which monitor the concentrations of particular substances in the brain, such as glucose, to diagnose Alzheimer's disease before its symptoms become severe. The primary fuel brain cells use is glucose; the more active a cell is, the more glucose it consumes. Less and eventually no glucose is used by sick and dying brain cells.

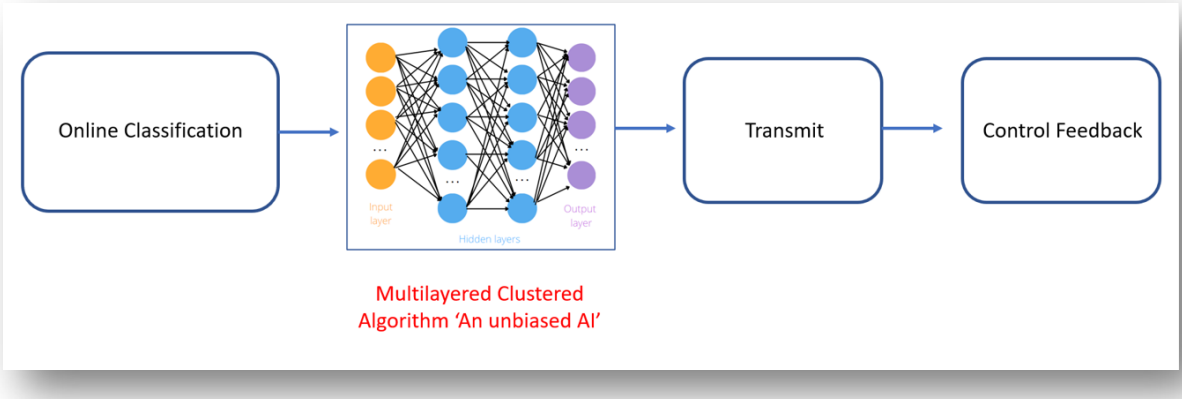
In other PET scans, proteins connected to Alzheimer's disease are searched for. However, because glucose PET scans are also used for cancer staging, they are far more prevalent and affordable, particularly in smaller healthcare facilities and impoverished nations. Radiologists have utilised these scans to check for decreased glucose levels throughout the brain, particularly in the frontal and parietal lobes, to identify Alzheimer's disease. The variations in glucose are minimal and challenging to detect with the naked eye, though, as the disorder steadily worsens over time.

To better diagnose Alzheimer's disease in its early stages, utilising PET scans, researchers used a machine learning method. Researchers supplied images from the Alzheimer's Disease Neuroimaging Initiative (ADNI), an enormous public dataset of PET scans from individuals who were ultimately diagnosed with either Alzheimer's disease, moderate cognitive impairment, or no diagnosis, to the algorithm to train it. After a while, the algorithm started to figure out which characteristics are necessary for accurately diagnosing Alzheimer's disease and which ones are not.

The researchers evaluated the algorithm on two brand-new datasets after it had been trained on 1,921 scans to gauge its performance. The first was 188 photos the algorithm had yet to see from the same ADNI collection. The second was an entirely new set of scans from 40 patients who had visited the UCSF Memory and Aging Institute with potential cognitive impairment (ucsf.edu). The algorithm performed brilliantly. In the first test set, 92% of patients who later had Alzheimer's disease were accurately diagnosed, and in the second test set, 98% were. Also, on average, it correctly predicted these events 75.8 months before the patient's ultimate diagnosis, or more than six years. According to researchers, the system must be tested and calibrated using more extensive, varied datasets from various institutions and nations.

The Proof of Concept





The Software Product Management Canvas

Problem

1. **Dementia/ Alzheimer's disease detection**
2. **Disease progresses very slowly**
3. **MCI patient differentiation**

Existing Alternatives

1. A detailed patient history
2. Information from family and friends
3. Physical and neurological exams and lab tests
4. Neuropsychological tests
5. Imaging tools such as CT scan, or magnetic resonance imaging (MRI). PET scans are used primarily for research purposes

Cost Structure

1. Product Development
2. Marketing expenses
3. Salaries

Solution

1. Functional MRI to detect BOLD Signal
2. Multilayered clustered Algorithm 'Unbiased AI'
3. Detect approx. 6 years earlier than diagnosis of clinical symptoms

Key Metrices

1. Process efficiency
2. Program efficiency
3. Longitudinal Patient data to train algorithms

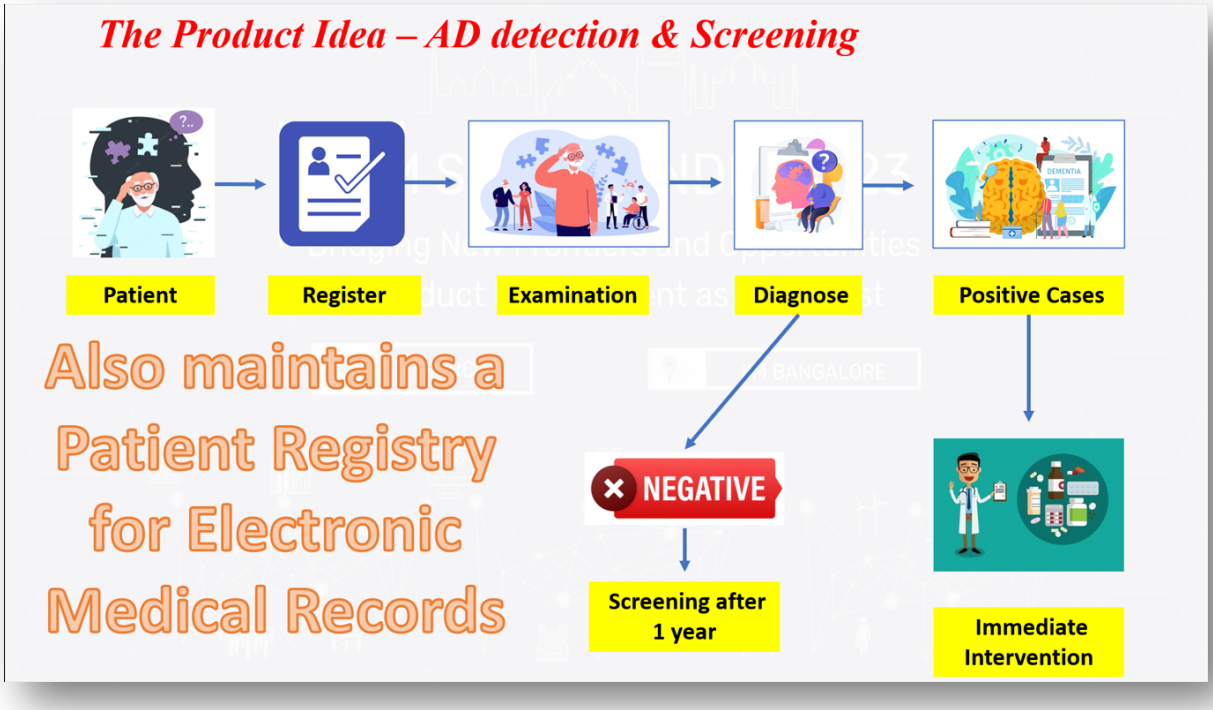
Unique Value Proposition

1. Early detection, halt disease progression

Customer Segmentation

1. Mental Hospitals
2. Psychologists/ Psychiatrists
3. Consultant Physicians

The Product



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