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AN INVESTIGATION OF AVAILABLE MEDICAL IMAGING DATA FOR THE EARLY DETECTION OF NEURODEGENERATIVE DISEASES

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ABSTRACT

Dementia is characterized by the acquired loss of cognitive and emotional abilities to an extent that it interrupts and inconveniences everyday life. It is not a disease, but rather, is used to describe a group of symptoms that occur when the brain cells stop working properly. Dementia has a prolonged onset period and can go unnoticed for years before significant symptoms manifest or a diagnosis. An early diagnosis for patients with dementia or its subtypes could open the door to better treatment and care as well as give patients the time and opportunity to plan their future while they still can do so. Neuroimaging techniques such as brain magnetic resonance imaging (MRI) and positron emission tomography (PET) are currently used as one of the 'gold standard' tools for diagnosing dementia causing diseases. However, these methods can be invasive, carry a risk to the patient, are time consuming and a burden on healthcare and financial resources. For this reason, the Early Detection of Neurodegenerative diseases (EDoN) initiative aims to develop an alternate approach for the large-scale early identification of individuals at risk for dementia causing diseases in a low burden, cost effective manner. EDoN is collecting digital data (e.g., from wearables and smartphone apps) and low burden clinical measures (e.g., blood tests) to use with machine learning models that can detect specific dementia causing diseases decades before noticeable cognitive symptoms manifest.

In order to validate the new detection methods and digital biomarkers developed within EDoN, a comparison against the 'gold standard' biomarkers coming from neuroimages is needed. In this report we provide an overview of medical imaging data relevant to dementia causing diseases. We explore the availability of neuroimaging data from databases that provide access upon request. We elaborate on the challenges of accessing the data and give the details of those databases we were able to gain access to, in terms of number of subjects as well as their age and gender, and the imaging modalities used.

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CONTENTS

CONTENTS

GLOSSARY/ABBREVIATIONS

AD	Alzheimer's Disease
APOE	Apolipoprotein E
ASL	Arterial Spin Labelling
bvFTD	behavioural variant Frontotemporal Dementia
Clinical Anchor	Outcome changes that are anchored/ linked to other clinical changes or results.
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DATSCAN	Dopamine Transporter Scan
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion Tensor Imaging
EDoN	Early Detection of Neurodegenerative Diseases
EP	Echo Planar imaging
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar Dementia
GR	Gradient Echo
GRAPPA	Generalized Auto calibrating Partially Parallel Acquisitions
Hypometabolism	Physiological state of having decreased metabolic activity due to decreased brain glucose consumption.
Hypoperfusion	Decreased blood flow through an organ
IDA	Image and Data Archive
LONI	Laboratory of Neuro Imaging
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient
MRI	Magnetic Resonance Imaging
nfvPPA	Nonfluent variant Primary Progressive Aphasia
NIfTI	Neuroimaging Informatics Technology Initiative
PD	Parkinson's Disease
PET	Positron Emission Tomography
PiB	Pittsburgh B compound
SE	Spin Echo
SPECT	Single Photon Emission Computed Tomography
SUVR	Standardized Uptake Value Ratio
svPPA	semantic variant Primary Progressive Aphasia
VaD	Vascular Dementia

1. INTRODUCTION

Dementia is a clinical syndrome that usually manifests as a symptom of an underlying disease. The term itself is not disease-specific, but rather used to describe a group of symptoms including an impaired ability to think, remember, or make decisions that interferes with everyday life. Dementia may be acute or chronic in nature and has a prolonged onset period. This means dementia causing diseases can go unnoticed for years or even decades before significant symptoms manifest or a diagnosis can be made. People who develop dementia before the age of 65 are said to have early onset dementia, and those affected post this age are said to have late onset dementia.

While the cause for dementia remains unknown, it is certain that dementia-causing diseases can induce structural and chemical changes in the brain leading to neuronal loss and brain volume shrinkage[1]. Dementia is associated with tangles and plaques in the brain, loss of connections, inflammation and eventual death of brain cells and is hence classified as a neurodegenerative disorder. As the disease progresses, more brain cells die causing further structural and functional changes to the brain[2]. Alzheimer's disease (AD) is the most common cause of dementia in western countries corresponding to 60% of the cases. Vascular dementia (VaD) comes in second contributing to about 20% of all cases, however due to similar symptomology and pathophysiology, AD and VaD are hard to distinguish. In AD, the causes and progression of degeneration are not well defined. Further kinds of dementia such as Lewy body dementia, Frontotemporal dementia, mixed dementia etc. are also characterised by degeneration of different structures in the brain.

An early diagnosis for patients with different disease subtypes could enable better treatment and care as well as give patients the time and opportunity to plan their future while they still have the capacity to do so. Neuroimaging techniques such as brain magnetic resonance imaging (MRI) and positron emission tomography (PET) are currently used as one of the 'gold standard' tools for diagnosing dementia causing diseases and can also help find evidence of other sources of damage to the brain such as tumours or strokes that may aid diagnosis and treatment. Cerebrospinal fluid and blood-based biomarkers are also used to provide a diagnosis. However, these methods can be invasive, carry a risk to the patient, are time consuming and a burden on healthcare and financial resources. Additionally, these methods may not be applicable to patients (e.g., patients with pacemakers cannot undergo MRI scanning) or easily available to patients due to lack of medical resources or financial resources to undergo these procedures. For this reason, the Early Detection of Neurodegenerative diseases (EDoN) initiative aims to develop an alternate approach for the large-scale early identification of individuals at risk for dementia in a low burden, cost effective manner[3]. EDoN is collecting digital data (e.g., from wearables and smartphone apps) and low burden clinical measures (e.g., blood tests) to use with machine learning models that can detect specific dementia-causing diseases decades before noticeable cognitive symptoms manifest.

To validate the new detection methods and digital biomarkers developed within EDoN, a comparison against the 'gold standard' biomarkers coming from neuroimages is needed. For this reason, EDoN will collect retrospective dementia cohort data from the patients who were diagnosed with imaging biomarkers. These data will be used to validate the new digital biomarkers and models developed within EDoN.

To alleviate the issues associated with accessing sensitive clinical data, in this work we explore the availability of neuroimaging data in access-upon-request databases. We list challenges of accessing medical imaging data and give the details of those databases we were able to access, including number of subjects, their age and gender, and the imaging modalities used. We also describe the EDoN cohort data that we will have access to in the short-term future. A

high-level overview of biomarkers, types of neuroimaging and treatment strategies for dementia is provided.

2. BIOMARKERS AND TREATMENT

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes. It could also be pharmacological response to a therapeutic intervention[4]. Assessing biomarkers is crucial to early detection of diseases that cause dementia whose symptoms manifest only after many years after the disease's onset.

2.1. Types of Biomarkers

Neuroimaging is one of the most common diagnostic procedures for detecting dementia causing diseases. Structural neuroimaging modalities such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans can assess *vascular damage*. *White matter signals* may also change over time for a variety of reasons which may or may not be related to neurodegeneration, which is reflected in structural images of the brain. These modalities can be used to identify regions of *atrophy* in the brain that reflect *neuronal loss*, a marker that is incorporated into the diagnostic criteria for several neurodegenerative diseases. The *rates of atrophy* can be used as proxy markers for neurodegeneration as well. While no structural imaging features have perfect sensitivity and specificity for any given diagnosis, there are some which provide positive predictive value and help to narrow the differential diagnosis to the most likely underlying pathologies[5]. Functional and Nuclear imaging through modalities such as Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) enables the quantification of patterns of the brain's *hypometabolism* and *hypoperfusion*. The manifestation of these patterns are characteristic to the underlying neurodegenerative disease type[6]. Functional Magnetic Resonance Imaging (fMRI) scans measure intrinsic fluctuations in *regional cerebral blood flow* using a linked blood-oxygen-level-dependent (BOLD) signal change in the magnetic properties of the cerebral blood flow in response to a particular task or stimulus.

Extracting fluid biomarkers is usually an invasive process which requires taking a sample of the tissue, organ, or fluid for testing. Cerebrospinal fluid (CSF) examinations are often recommended for individuals with cognitive impairment under the age of 55, for individuals with unusual disease progressions or for those who are immunosuppressed[7]. CSF analysis using immunochemical techniques can help with the measurement of a range of *neuronal-specific or neuronal-enriched proteins* such as β-amyloid and tau levels. *Amyloid levels* especially, have been extensively researched in AD patients. The Alzheimer's Disease Neuroimaging Initiative (ADNI), the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for the diagnosis of AD, 328 of 341 (96%) clinically diagnosed with AD dementia patients were amyloid-positive. This subsequently suggests that the use of *β-amyloid* as a biomarker and amyloid imaging can extend a very high rate of diagnostic accuracy[8]. At the same time, it is worth noting that the collection and use of these markers differ significantly between clinicians, laboratories and countries[5].

2.2. Risk factors

There is a wide range of risk factors for dementia, but its root cause is unknown and is dependent on the underlying disease. One of the most predominant factors to assess a patient's risk of dementia is the presence of the APOE gene. Its presence along with several of its alleles increase the risk for late onset dementia[9]. There are also several lifestyle factors that may increase an individual's risk to dementia such as physical activity, smoking, alcohol consumption and Body Mass Index. Comorbidities have also been linked as risk factors for

dementia. Diseases like hypertension may indicate as an important risk factor for VaD, while Type 2 diabetes may indicate as an important risk factor for AD.

Since dementia is a symptom of underlying disease, and manifests for a wide array of diseases, understanding the risk factors and connecting them to the pattern of progression of the underlying disease is crucial to an early diagnosis.

2.3. Treating dementia

The first line of treatment for most dementia involves the administration of Cholinesterase inhibitors. They are also the main treatment for dementia caused by AD. This treatment is a response to cognitive decline and there is documented evidence to suggest patients benefit from its prescription. Cholinesterase inhibitors result in higher concentrations of acetylecholine leading to increased communication between nerve cells which in turn may temporarily improve or stabilise the symptoms of dementia. Although this is not a cure nor does this work for everyone. It approximately follows a rule of thirds where one third of patient's state of dementia do not deteriorate further, one third is observed to have no difference upon drug administration and one third of the patients deteriorate at a rate as if untreated[10]. This does not slow the progression of the underlying disease or cure it either. Cholinesterase is not administered in patients diagnosed with VaD.

Recently, a humanized monoclonal antibody targeting amyloid protofibrils has been developed called Lecanemab. It targets early treatment of AD. In its phase II trials, Lecanemab reduced amyloid accumulated in the brain and slowed progression on key global and cognitive scales evaluating efficacy after 18 months of treatment. Since the treatment slowed progression, it did extend the duration of Mild Cognitive Impairment (MCI) due to AD and mild AD dementia and shortened duration in moderate and severe AD dementia. For further information on this novel drug, we refer readers to the following texts[11,12].

There are preventive measures that can reduce one's risk to developing dementia later in life, known as modifiable risk factors. These include lifestyle changes such as increasing physical activity, adopting a balanced, nutritious diet, quit smoking, decreasing alcohol consumption, maintaining a healthy blood pressure etc.

3. DEMENTIA AND NEUROIMAGING

Brain imaging is a common diagnostic tool in the evaluation of dementia. Since neurodegenerative diseases are associated with the development of pathological changes long before the development of functional impairment, neuroimaging has an important role in the diagnosis of early onset of dementia[13]. This section outlines the role various imaging modalities play in the detection, assessment and treatment of different dementia causing disease subtypes.

3.1. Structural imaging

Structural imaging modalities can help reveal structural abnormalities in the brain associated with early onset of dementia. It can also help rule out the presence of other disease with symptoms that may be mistaken for dementia.

CT scans are a common part of first level examinations for patients with suspected dementia or Mild Cognitive Impairment (MCI). CT scans can provide insights into detecting common causes of secondary dementia, which is a form of dementia that develops as a peripheral condition to a pre-existing mental illness or physical condition. CT scans can detect causes of cognitive decline as well. They help identify tumours or lesions in the brain that may be causing

cognitive decline as well as detecting and quantifying vascular changes in the brain associated with VaD[14]. CT scans may also be used with contrast dyes to rule out alternate pathologies. CT imaging is usually adopted in more acute settings or in clinics that do not have access to MRI scans.

MRI scans are preferred when quantifying volumetric changes that take place because of neurodegeneration. MRI scans have been used to study patients with Mild Cognitive Impairment (MCI) who are at high risk to progress to AD. These studies have shown that hippocampal volumes and cortical volumes in the parietal and lateral temporal regions are able to predict the likelihood of progression. Longitudinal studies have also demonstrated that patients with MCI have higher rates of atrophy in the temporal lobe[5]. These structural changes are highlighted when the patient undergoes MRI scanning.

Diffusion Tensor Imaging (DTI) is a structural imaging modality that measures the diffusion properties of water molecules in the brain and is useful in visualising white matter tracts that connect different regions of the brain. DTI is adept in measuring microstructural changes occurring in the brain due to a dementia causing disease. This enables the assessment of the integrity of white matter tracts and can reveal injuries that may not be apparent in other imaging modalities[15]. For further applications of structural imaging, we refer the reader to these texts[10,13,15–18].

3.2. Functional imaging

Functional imaging provides insights to the functional operations of the brain. Functional brain pathology appears in the brain much before structural abnormalities may be detected. Thus, functional imaging may be better suited to the early detection of dementia causing diseases. Scanning modalities such as PET or fMRI can reveal metabolic abnormalities in a structurally normal brain. Classic abnormalities associated with hypoperfusion or hypometabolism appear to be present prior to the onset of dementia symptoms but can predict progression to AD. These can be detected through longitudinal functional imaging modalities which highlight functional changes as they occur. Complete applications of functional imaging for dementia can be found in these texts[6,13,19–21].

3.3. Nuclear Imaging

SPECT is a nuclear imaging modality used frequently in diagnostic medicine. It allows clinicians to assess the perfusion and functionality of specific tissues. SPECT imaging involves the administration of radioactive tracer compounds (radioactive isotopes) coupled with biologically active ligands specific to the tissue being imaged. Compounds used for imaging the brain are directly correlated with metabolic activity, allowing cerebral SPECT studies to highlight areas of increased or decreased brain activity as well as areas of anatomically normal or damaged brain tissue that may not be apparent on conventional imaging modalities. For more information on nuclear imaging, we refer readers to these texts[13,22].

USING 18-F PET WITH FLORBETAPIR OR FLUTAMETAMOL:

18-F Florbetapir (Also known as the PiB Pittsburgh compound) is a radiopharmaceutical that is used in PET scans as a tracer that binds to amyloid – β plaque deposits in the brain. The radioactive compound breaks down releasing energy that is detected by a PET scanner. 18-F Florbetapir is administered via injection and images can be acquired 50 minutes post injection. In the first and second phase of clinical trials, Florbetapir clearly differentiated between patients with AD from healthy controls[23]. Results from phase three confirmed strong correlation between Florbetapir PET images and post-mortem assessment of amyloid β deposition. This data is then represented as a Standardized Uptake Value Ratio (SUVR) which

helps distinguish normal levels of uptake from abnormal levels. SUVR is defined as the ratio of activity per unit whole body volume and is considered a semi quantitative parameter[24].
1F-18 Flutametamol is another radiopharmaceutical derived from PiB that is also used to detect β – Amyloid deposits upon PET scans. It is intravenously administered and selectively accumulates and binds to cerebral fibrillar amyloid β in the brain (also referred to as amyloid β deposits). 18 F Flutametamol PET may also be combined with structural MRI for categorizing disease[25].

4. NEUROIMAGING DATABASES

The databases presented in this report were found on the Image and Data Archive at the Laboratory of Neuro Imaging[26] (IDA LONI). The IDA was initially created with the incentive to anonymise and collect neuroimaging data for the International Consortium for Brain Mapping study (ICBM) in which MRI and PET scans from 850 normal adult subjects were collected at three North American Sites. The IDA was later expanded with the growing interest in biomedical data to include data associated with Neurological conditions. As of 2023, the IDA has become a global resource for storing and disseminating neuroimaging, clinical, biospecimen and genetic data for a growing number of national and international consortia efforts for both small and large scale studies[26]. The databases covered in this report are available publicly on the IDA, upon request. This section elaborates on the cohorts that are relevant to EDoN's research. Table 1 provides an overview.

Table 1: Summary of medical imaging databases and data available upon request

Database	Neurodegenerative disease targeted	MRI	fMRI	PET	DTI
A-4 Anti Amyloid Treatment in Asymptomatic Alzheimer's	Alzheimer's Disease	7676	1668	4933	1724
Australian Imaging Biomarkers and lifestyle	Alzheimer's Disease	4011	-	1575	-
Parkinson's Progression Markers Initiative	Parkinson's Disease	9456	1880	655	4435
Alzheimer's Disease Neuroimaging Initiative	Alzheimer's Disease	90,824	8787	9633	7829
Neuroimaging in Frontotemporal Dementia	Frontotemporal Dementia	11,158	3394	165	4269

4.1. A4: ANTI AMYLOID TREATMENT IN ASYMPTOMATIC ALZHEIMER'S

The objective of this study was to clarify the preclinical stage of AD by estimating when β amyloid[8,27,28] accumulation first becomes associated with changes in cognition. According to the study, to optimize early interventions against AD, it is necessary to understand the transition from purely asymptomatic AD into the clinical stage of the disease. However, the thresholds for cognition that define mild cognitive impairment (MCI) or dementia are insufficient to capture subtle changes in cognition[29]. The study tests how 18F-florbetapir levels were related to subtle cognitive dysfunction in multiple domains in 4432 participants who were screened for the A4 trial.

4.1.1. Participants

Participants were included in the trial if they (1) completed an 18F-florbetapir PET scan, (2) had an APOE genotype information, (3) completed a battery of neuropsychological testing, (4) scored between 25 and 30 on the Mini Mental State Examination (MMSE), (5) had a clinical dementia rating of 0, and (6) were between the ages of 65 and 85. Participants were excluded from the A4 study if: (1) they were taking a prescription Alzheimer's medication, (2) had a current serious or unstable illness (for a full description please refer to the text[29]) , (3) if they had a history of serious infection affecting the brain or head trauma resulting in protracted loss of consciousness, (4) had a history in the last 5 years of a primary or recurrent malignant disease (refer text for full description[29]), (5) had a history of Human Immunodeficiency Virus (HIV), (6) were at serious risk of suicide or have a history in the last two years of depression or bipolar disorder, (7) had a history in the last 5 years of chronic alcohol or drug dependence or abuse, (8) were residing in a skilled nursing home.

4.1.2. Image Acquisition

Amyloid PET images were acquired using 18F-florbetapir[30], acquired 50 – 70 minutes post-injection. Images are realigned and averaged and spatially registered to the standard image space. This is step is crucial to ensure that when two scans are compared (which may be from the same patient or different patients), the points on the image planes correspond to the same anatomical location. The data was then sampled in a global neocortical region for β- Amyloid and was expressed as a Standardized Uptake Value Ratio (SUVR) with a cerebellar reference region[29,31]. A β- Amyloid negative group was defined as participants with 18F-florbetapir PET SUVR < 1.10[29,32].

MRI scans include T1-weighted images as well as T2-weighted images. The T1-weighted images are subject to GradWarp[33] algorithms which is a system specific correction of image geometry distortion due to gradient non-linearity. The degree to which images are distorted due to gradient non-linearity varies with each specific gradient model. This correction algorithm is essential to MRI scans as they are acquired with the Magnetization -Prepared Raid Acquisition Gradient Echo[34] (MPRAGE) method. The images are also DeFaced[35], which refers to the protocol adopted to fully anonymize an MR brain image. T2-weighted images are acquired as T2* images or T2-FLAIR images. For more information about acquisition protocol and algorithms we refer the readers to these texts[33–35].

The participants also completed neurophysiological battery tests including Preclinical Alzheimer's Cognitive Composite, comprising of the Mini Mental State Exam (MMSE) as a measure of global cognition, Logical Memory Delayed Recall, a narrative recall memory test, Free and Cued Selective Reminding Test, a list recall memory test, the digit symbol substitution test as a measure of executive function. Further information about the cognition tests and their designs are elaborated here[29].

4.1.3. Data Available

As of 27th April 2021, the neuroimaging datasets for MRI, amyloid and tau PET (for a subset of participants) are available on the IDA upon request.

All 7676 pre-processed MRI images (either T1-weighted or T2-weighted) are available as NIfTI (Neuroimaging Informatics Technology Initiative) files for download.

As mentioned above, all 4933 PET scans were acquired using 18F-florbetapir. The pre-processed images are available for download as DICOM files.

Additionally, there are 1668 resting state fMRIs available acquired with the subject's eyes open. The pre-processed images can be downloaded from the IDA as DICOM files.

There are 1724 Diffusor Tensor Imaging files available as well acquired along the axial plane. The pre-processed images can be downloaded from the IDA as DICOM files.

Metadata associated with the imaging data collection is available for download from the IDA.

4.2. AUSTRALIAN IMAGING, BIOMARKERS AND LIFESTYLE

The Australian Imaging, Biomarker and Lifestyle (AIBL) flagship study aimed to prospectively research AD in 1000 individuals aged over 60 to improve the understanding of the pathogenesis of AD, while focusing on methods for early detection. The study hypothesized that retrospectively cross-referencing blood biomarkers with both longitudinal and cognitive measures and the presence or absence of brain amyloid detected by Pittsburgh B compound (PiB) PET scanning would enable the identification of blood biomarkers which detect AD prior to the emergence of clear cognitive symptoms[36].

4.2.1. Participants

The study sought to characterize 1000 individuals from the following groups[36]:

- At least 200 individuals diagnosed with AD.
- At least 100 individuals diagnosed with Mild Cognitive Impairment.
- At least 700 individuals without cognitive impairment including volunteers with at least one copy of the APOE ε4 allele, volunteers without a copy of the APOE ε4 allele and volunteers who expressed subjective concern about their memory function.

A total of 1166 volunteers were recruited out of which 54 were excluded from further study due to comorbid disorders which could affect cognition or due to withdrawal of consent. The participants were reassessed at 18-month intervals to determine the predictive utility of various biomarkers, cognitive parameters, and lifestyle factors as indicators of AD.

4.2.2. Image Acquisition

Until the 36-month mark, AIBL subjects with MR and PET imaging data constitute about 25% of the full AIBL cohort. At 54 months, the image database was enriched with 250 MR/Flutemetamol, 200 MR/Florbetapir and 50 MR/PiB. 3D T1 MPRAGE and T2 turbospin echo and FLAIR sequence MRI were acquired for screening and co-registration with PET images[37].

Subjects received MRI scans using ADNI 3D MPRAGE sequence field strength of 3.0 T. T2 fast spin echoes and FLAIR sequences were obtained as well.

Subjects also underwent PET scanning ~370 MBq C-PiB IV over 1 minute. A 30-minute acquisition in 3D consisting of 6 frames each of 5 minutes, starting 40 minutes after injection of PiB was performed. Additionally, a transmission scan was performed for attenuation correction. PET images were reconstructed using a 3D Ramla algorithm and the PET data was corrected for partial volume effects using a 3-compartment model. For a description of the model, we refer the readers to these texts[28,37].

4.2.3. Data Available

There are 4011 MRI scans with the modalities mentioned above. These are original images prior to pre-processing and can be downloaded from the IDA as DICOM files.

There are 1575 PET scans acquired as per the imaging procedures mentioned in the previous section and can be downloaded from the IDA as DICOM files.

Metadata elaborating the imaging data collected is available on the IDA upon request.

4.3. PARKINSON'S PROGRESSION MARKERS INITIATIVE

The Parkinson's Progression Marker Initiative (PPMI) is an observational, international, multi-centre study designed to identify Parkinson's Disease (PD) progression biomarkers to improve the understanding of PD and in due course, provide tools that enhance the likelihood of success of PD therapeutic trials. The objectives of the study were to (1) establish standardized protocols for acquisition, transfer, and analysis of clinical, imaging and biospecimen data that can be used for research purposes, (2) investigate the existing clinical, imaging and biospecimen PD progression markers that individually, or in combination, will rapidly demonstrate interval change in PD patients in comparison to healthy controls, or in subsets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging or biospecimen change, (3) optimize bioassays and conduct preliminary verification studies on promising biological markers using stored biospecimen[38]. The end goal of the study was to track progression both before and after initiation of commonly used symptomatic PD medications.

4.3.1. Participants

As of 2011, the PPMI cohort was designed to comprise of 400 recently diagnosed with PD and 200 healthy subjects followed longitudinally for biomarker assessment. As of 2020 close to 4000 participants are enrolled at about 50 sites worldwide.

The biological samples include the longitudinal collection of biomarkers from blood, CSF and urine samples stored in a biorepository that is available upon application to an independent PPMI biospecimen review committee through the IDA or PPMI website. The PD subjects are recruited at a disease threshold where they must display at least two symptoms from bradykinesia, resting tremors and or rigidity with diagnosis within two years and to be untreated for PD. All subjects will undergo dopamine transporter imaging (DAT imaging) and a DAT deficit is required to be considered as an eligible PD subject for the study. Healthy subjects should have no significant neurological dysfunction, no first-degree family member with PD and a Montreal Cognitive assessment[39] MoCA > 26. The MoCA test was developed based on the clinical intuition regarding domains of impairment commonly encountered in MCI, adapted to a screening test. PET scans as well as single photon emission computerized tomography (SPECT) scans, fMRI, MRI, CT and DTI scans are acquired at 21 clinical study sites (16 in USA and 5 European) for the PPMI study. All sites have undergone training to ensure standardization of data acquisition and biospecimen collection[38].

Evaluations occur at the time of screening/baseline and at 3-month intervals during the first year of participation and then every 6 months thereafter.

4.3.2. Image Acquisition

All subjects diagnosed with PD underwent longitudinal DAT imaging to monitor the change in DAT density during the study. A subset of the patients also underwent longitudinal MRI and DTI although MRI and DTI screening was restricted to sites with uniform camera and image acquisition systems to enable standardisation of longitudinal data.

T1-weighted MRI images were acquired with a 3.0 T field strength, and pulse sequence = GR. An MPRAGE GRAPPA protocol was adopted. GRAPPA or 'Generalized Auto calibrating

Partially Parallel Acquisitions' is an image reconstruction technique that allows Fourier domain reconstructions of data sets that are sampled along 2 dimensions[38,40]. This technique is an extension of the simultaneous acquisition with spatial harmonics[40,41] (SMASH).

T2-weighted MRI images acquired (with either a T2 or a T2 FLAIR modality) with a field strength of 1.5 T or 3.0 T and a field view of 512 X 512 pixels, pulse sequence = SE and with a slice thickness of 5.0 mm or 3.0 mm.

An EP2D Resting state fMRI scans were collected with a slice thickness of 3.3 mm and a field view of 476.0 X 462.0 pixels, and pulse sequence = EP.

PET scans were acquired using F-18 radioisotope with a slice thickness of 2.4 mm. Some images were subject to scatter correction where applicable.

Spectral images were acquired using DAT imaging. A reduction of striatal uptake would suggest the presence of PD in the patient which can be captured through DAT imaging. DAT may also have prognostic value for disease progression as well[38,42,43].

DTI images were acquired with a field strength of 3.0 T, gradient directions = 64.0, pulse sequence = EP and slice thickness = 2.0 mm.

4.3.3. Data Available

There are 6365 T1-weighted MRI original images available and can be downloaded from the IDA as DICOM files.

There are 3091 T2-weighted MRI original images available and can be downloaded from the IDA as DICOM files.

There are 655 PET scans available as original images and can be downloaded from the IDA as DICOM files.

There are 3391 SPECT scans available as original images and can be downloaded from the IDA as DICOM files.

There are 1880 resting state fMRI scans available as original images and can be downloaded from the IDA as DICOM files.

There are 4435 DTI scans available as original images and can be downloaded from the IDA as DICOM files.

Metadata elaborating the imaging data collected is available on the IDA upon request.

4.4. ADNI: ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

The ADNI initiative was launched in 2004 with the aim of characterizing AD by the accumulation of β-amyloid and phosphorylated tau, synaptic loss and neurodegeneration that leads to cognitive decline.

In this section we focus on ADNI3 which was launched in 2016.

4.4.1. Participants

ADNI participants as per the IDA were stratified into the following groups: Cognitively Normal (CN), Significant Memory Concern (SMC), Early Mild Cognitive Impairment (EMCI), Alzheimer's disease (AD), Late Mild Cognitive Impairment (LMCI), Mild Cognitive Impairment (MCI) and consisted of 5,141 subjects in total.

4.4.2. Image Acquisition

An MRI core is responsible for all aspects of MRI images. Including determining pulse sequence, site qualification, tracking MRI data acquisition and processing and the performance of all MRI processing. The functions of ADNI MRI core falls into three categories: (1) those of the central MRI laboratory at Mayo Clinic, needed to generate high quality data in all subjects at each point (2) those of the funded ADNI MRI core imaging analysis groups responsible for analysis of MRI data and (3) the joint function of the entire MRI core in designing the problem and solving MR acquisition, pre-processing, and analyses methods. The MRI protocol was modernized and extended to all newly enrolled participants of ADNI-GO and ADNI -2 subjects and beyond. These scans were acquired at 3.0 T with a core set of three sequence types: 3D T1-weighted volume, FLAIR and long TE gradient echo volumetric acquisition[44]. The study also involved acquiring resting state fMRIs to assess functional connectivity and DTI imaging as well.

The MRI scans followed the 3D T1-weighted MPRAGE sequence, which is explained in the previous sections. The MPRAGE sequence was also repeated back-to-back in ADNI-1 to increase the likelihood of acquiring at least one high quality MPRAGE scan. Additionally, the T2-weighted scan (proton density weighted/ dual fast spin echo) was acquired at each point to evaluate the presence of vascular diseases or detection of general pathology[44]. Scans were acquired at 1.5 T and a subset of subjects were involved in scans at 1.5 T and 3.0 T. MRI scans were acquired with a field view of 256 X 256 pixels and with a slice thickness of 1.2 mm.

ADNI VERSION PROTOCOL COMPATIBILITY:

The ADNI cohort has evolved over the years. With each version, changes are implemented to improve the imaging data. This section outlines the changes between the latest ADNI3 version to previous versions. The ADNI3 protocol was aimed at modernization. Listed below are the modifications implemented in the ADNI3 protocol with respect to older versions[45]:

- 3D T1 – Improved spatial resolution in ADNI 3 (improved to 1mm cubed). This is believed to not have a significant effect on longitudinal in person analysis.
- FLAIR – changed from 2D to 3D in ADNI3. This results in significant improvement in spatial resolution, and additionally has a change in contrast model. This data is claimed to be incomparable to ADNI2 data unless subject to significant image processing to account for differences in acquisition.
- GRE2- No change in this data in ADNI3 and is compatible to ADNI2 data.
- High resolution coronal for hippocampal subfields- claimed to be compatible with ADNI 2 as there are no significant changes.
- ASL – 2D PASL was used in ADNI2, and 3D (PASL or pCASL which is a quantitative method for non-contrast assessment of blood flow) are used wherever possible in ADNI3. This data is claimed to be incompatible with earlier versions of ADNI.
- DTI - ADNI3 uses 2.0 mm isotropic voxels, but ADNI2 used 2.7 mm, with b = 0 and 1000 s/mm^2 weighted volumes. ADNI3 Basic and Advanced both provide b = 0 and 1000 s/mm^2 weighted volumes. Since this is different than ADNI2, it would have to be corrected for before subject to comparison.

fMRI – Basic ADNI2 and ADNI3 are claimed to be compatible with no significant changes but advanced versions are incompatible. For more details on image acquisition protocols and the ADNI information, we refer readers to this text[45].

4.4.3. Data Available

There are 65,908 T1-weighted MRI scans available as original images and can be downloaded from the IDA as DICOM files

There are 24916 T2-weighted MRI scans available as original images and can be downloaded from the IDA as DICOM files.

There are 9633 PET scans available as original images and can be downloaded from the IDA as DICOM files.

There are 7829 DTI scans available as original images and can be downloaded from the IDA as DICOM files.

There are 8787 resting state fMRI scans available as original images and can be downloaded from the IDA as DICOM files.

Metadata elaborating the imaging data collected is available on the IDA upon request.

4.5. NEUROIMAGING IN FRONTOTEMPORAL DEMENTIA

The Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI) is a study funded by the National Institute of Ageing. The primary goals of the FTLDNI were to identify neuroimaging modalities and methods of analysis to track Frontotemporal Dementia. It also aimed to assess the value of imaging against other biomarkers for diagnostic purposes[46]. This study is also referred to as the NIFD or the Neuroimaging in Frontotemporal Dementia study.

4.5.1. Participants

The study encompassed over 120 patients with FTLD, including 60 with bvFTD, 30 with svPPA, 30 nfvPPA subjects and 75 healthy controls each of whom would have three clinical assessments over one year along with MRI and PET scans acquired at each assessment[47].
FDG – PET scanning was obtained for as many subjects as possible depending on their willingness and ability to participate in additional scans

4.5.2. Image Acquisition

The clinical protocol was designed to enable tracking of the disease using measures that could potentially be used in clinical trials of FTLD which include cognitive and functional measures[47]. The MRI scans were acquired at 3 T and included T1-MPRAGE, FLAIR, DTI, ASL perfusion imaging and resting state fMRI. The parameters were chosen to match those returned by the ADNI cohort (and is extended to accommodate newer versions of the ADNI cohort). Amyloid PET with Pittsburgh B compound (PiB) is available for most of the patients who underwent PET scanning[47].

4.5.3. Data Available

There are 6803 T1-weighted MRI scans available as original images to download from the IDA as DICOCM files.

There are 4355 T2-weighted MRI scans available as original images to download from the IDA as DICOM files.

There are 165 PET scans available as original images to download from the IDA as DICOM files.

There are 4269 DTI scans available as original images to download from the IDA as DICOM files.

There are 3394 resting state fMRI scans available as original images to download from the IDA as DICOM files.

Metadata elaborating the NIFD clinical data, and a data dictionary is available on the IDA upon request.

5. EDoN cohorts

The selection of EDoN cohorts to collect patient data was based on the kind of clinical data that cohorts were collecting and their specific inclusion/exclusion criteria. Relevant clinical data was prioritised due to the importance of clinical anchors in the assessment of accuracy of machine learning models. Table 2 provides a summary of the cohorts engaged with EDoN as of March 2023.

Table 2: Summary of cohorts with patient data recruited by EDoN

Cohort	Description
Amsterdam Dementia Cohort	The Alzheimer centre of the VU university Medical Centre (affiliated with the Vrije Universiteit Amsterdam) formed the Amsterdam Dementia Cohort with almost 6000 individuals. The study collected information about cognitive tests, memory tests, behavioural and psychological tests, executive functioning tests, language tests, visuo-spatial functioning tests as well as clinical evaluations[48].
Alzheimer's Disease Neuroimaging Initiative	ADNI's aim is to determine the relationships between clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of late onset AD. The studies strategy is based on the concept that AD can be characterized by the accumulation of A β, synaptic loss and neurodegeneration that leads to cognitive decline[45].
Australian Imaging Biomarkers and Lifestyle	The AIBL study aimed to recruit 1000 individuals aged over 60 with prospective research into AD. The participants had a diagnosis of either MCI, AD or healthy and were assessed at 18-month intervals. AIBL assessments comprise of extensive study of clinical factors and cognitive function, CSF, structural and A β neuroimaging, and data about daily lifestyle[36].
The Swedish BioFINDER Study II	The Swedish BioFINDER study consists of four cohorts where patients were prospectively followed longitudinally. The study aimed to develop methods for early and accurate diagnosis for AD and PD. The study also aimed to investigate the heterogeneity of dementia

	and parkinsonian disorders to develop a new pathology-based disease classification[49].
ALFA plus nested cohort study	ALFA+ is a cohort involved in prospective and observational study for the early identification of biomarkers of AD in 500 cognitively healthy people who are descendants of patients. The aim of the study is to describe biological processes and identify factors that may precede the clinical phase of AD. ALFA+ aims to analyse the association between biological, structural, functional, and neurocognitive brain markers that characterize the preclinical phase of the disease and its natural history[50].
Deep and Frequent Phenotyping protocol (DFP)	The DFP study is a repeated measures observational study where participants are recruited through existing parent cohorts. Repeated measures of both established and experimental modalities were performed. The study recruited male and female participants over the age of 60 with prodromal AD with cognitive impairment. AD pathology was assessed using PET imaging or CSF biomarkers[51].
Dominantly Inherited Alzheimer Network (DIAN)	DIAN is an international registry of individuals at risk of developing autosomal dominant AD. The study's primary aims were to investigate the temporal ordering of AD pathophysiological changes that occur in asymptomatic mutation carriers and to identify those markers that support the transition from cognitively normality and cognitive assessment[52].
ENLIS-UK	ENLIST-UK is a three-year longitudinal observational study on individuals diagnosed with Lewy Body Dementia, PD, or AD. The main objective was to examine the presence of core clinical features, pro inflammatory cytokines or CSF AD markers associated with an increased rate of cognitive decline[53].
Insight-46	Insight 46 is a neuroscience sub study of the MRC National Survey of Health and Development. This British birth cohort studies has followed 5362 individuals since their birth and have tracked them in 24 waves of data collection incorporating a wide range of health and functional measures, including repeat measures of cognitive function. The study protocol involves a prospective two time point (0, 24 month) data collection covering clinical, neuropsychological, β-amyloid PET and MRI scanning, as well as biomarker and genetic information[54].
National Alzheimer's Coordinating Centre (NACC)	NACC maintains a cumulative database including clinical evaluations, neuropathy data and MRI imaging. They are funded by the National Institute of Ageing (NIA) which appointed a clinical task force to determine and define an expanded standardized clinical dataset called the Uniform Data Set (UDS) to provide researchers with a standard set of assessment procedures collected longitudinally to better characterize Alzheimer's Dementia Cohort

	participants with mild AD and MCI in comparison to non demented controls[55].
UK Biobank	The UK Biobank aims to include 500,000 people from all around UK. The study intends to conduct prolonged follow ups with all the participants through routine medical and other health related records. This will allow the identification of comparatively large numbers of individuals who develop a wide range of disabling and or life-threatening conditions[56].

6. CONCLUSION

This report has investigated the availability of access upon-request databases with relevant clinical and patient data. It provides a brief insight into dementia, and risk factors for the diseases that cause it as well as biomarkers and their role in detecting dementia causing diseases. The report describes five medical imaging databases from the Image and Data Archive through which data from neurodegeneration studies can be accessed and downloaded: The A4 study, PPMI, ADNI, AIBL and NIFD studies that have collected longitudinal clinical data that can enable further research for the early detection of dementia. Since these are longitudinal databases, they can be used to detect various biomarkers for early signs of dementia as well as stratify subtypes of dementia based on structural and functional abnormalities. However, standardization of the image data is required before comparison of data between cohorts is possible, as the studies have different acquisition protocols for different modalities that must be taken into account. Future work could also include classification of the disease causing dementia based on the patients progression of neurodegeneration.

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