Cross-sectional analysis of FDG PET measured amygdala and parietal activity in patients with Alzheimer's disease and cognitive decline of unknown aetiology, for patients who may have limbic-predominant age-related TDP43 encephalopathy.



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Cross-sectional analysis of FDG PET measured amygdala and parietal activity in patients with Alzheimer's disease and cognitive decline of unknown aetiology, for patients who may have limbic-predominant age-related TDP43 encephalopathy.

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Abstract

Background: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently recognized cerebral proteinopathy that can lead to a clinical syndrome indistinguishable from Alzheimer's disease (AD) in the antemortem setting.

Objective: To assess the prevalence and degree of amygdala hypometabolism in elderly patients referred to a tertiary hospital for assessment of cognitive decline.

Methods: Retrospective cross-sectional exploratory analysis (for the period of 2010 to 2022) of two cohorts (60 to70 years old [y.o] and 80y.o and above). All subjects's data was retrieved from the Government of Western Australia Department of Health database, and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. A total of 348 subjects were used for this study.
We used standard uptake values ratios (SUVRs) to to quantify metabolic activity in the amygdala and parietal lobe region. The normal range of metabolic activity for the amygdala and parietal lobe regions was generated by taking the mean SUVRs ±2 standard deviations from our Normal group (cognitively assessed normal subjects for their age). Subjects below the normal range of metabolic activity *with only* amygdala but not parietal lobe reduction formed our suspected LATE cases. Subjects with only parietal lobe reduction formed AD cases, and subjects with the both amygdala and parietal reduction formed our suspected comorbid AD /LATE cases.

Results: Suspected pure LATE, and comorbid AD/LATE in subjects with CDUA and AD is more common in age group 80 and over than in age group 60 to 70, with presence in respectively 7% and 6.3% of cases. Overall prevalence of amygdala reduction in AD subjects was approximately 18% in age group 80 and over, and 23.5% in age group 60 to 70, which is similar to what is suggested in the literature (approximately 20% LATE).

Conclusion: Results support using measured amygdala activity as a technique to further categorise CDUA and AD patients to determine suspected LATE status.

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Lay Summary

Alzheimer's is a disease which affects memory, thinking and behaviour. Specific areas of the brain have been linked to the development of Alzheimer's disease, including the parietal lobe but sparing the amygdala. There are a multitude of diseases that mimic the symptoms of Alzheimer's disease but the majority have distinguishing features. However, it was discovered in a relatively new study that the TDP-43 protein can cause brain decline identical to Alzheimer's disease. This disease was termed limbic-predominant age-related TDP-43 encephalopathy and has been found to affect the amygdala initially and most severely with relative sparing of the parietal lobe. Therefore we predict pure Alzheimer's diseased subjects would experience abnormal parietal lobe metabolic reduction whereas limbic-predominant age-related TDP-43 encephalopathy subject would experience abnormal amygdala metabolic reduction and patients with a combination of both diseases would experience abnormal reductions in both regions.

Currently we are unable to differentiate between the proteins causing Alzheimer's and those that mimic Alzheimer's disease such as Lymbic predominant Age related TDP43 Encephalopathy, or provide a definitive way to see the proteins without invasive procedures.

In this study we aim to assess the usefulness of brain imaging to determine amygdala and parietal lobe FDG activity in patients with undiagnosable causes of worsening memory or Alzheimer's disease, as a predictor for limbic-predominant age-related TDP43 encephalopathy.

As TDP-43 is a disease which almost exclusively affects the very elderly we are studying two groups of patients (80 years old and older and 60 to 70 years old) with reduced mental capacity who had brain imaging done. We also took data from another database to create a standard of comparison.

We compared the activity of the amygdala and parietal lobe from the Alzheimer's disease group and cognitive decline of unknown aetiology group to the standard cognitively assessed normal group to see if we could identify subjects with features of amygdala and parietal lobe reduction which match the features of reduction of Alzheimer's disease, limbic-predominant age-related TDP43 encephalopathy and/or comorbidity of both.

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List of abbreviations

TDP-43	TAR DNA-binding protein 43
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LATE-NC	Limbic-predominant age-related TDP-43 encephalopathy neuropathological changes
SUVR	Standard uptake value ratio
ROI	Region of interest
FDG-PET	Fluorodeoxyglucose positron emission tomography
MRI	Magnetic resonance imaging
AD	Alzheimer's disease
CDUA	Cognitive decline of unknown aetiology
DPPO	Design population predictor outcome
DOS	Date of scan

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1 Introduction

1.1 Overview

Cognitive impairment is common, particularly in the elderly and is mostly due to a build-up of abnormal proteins in the brain that affect the neurons leading to abnormal function and eventually death of nerve cells.

The most common cause is related to amyloid build up, which contributes to the development of Alzheimer's disease (AD,) people with this disease typically present initially with memory loss. Other proteins, including tau and alpha-synuclein, tend to accumulate in different parts of the brain and lead to impaired neuronal function causing problems with other areas of brain function.

More recently a protein, TDP43, has been found to accumulate in the brains of elderly people who can subsequently develop symptoms of cognitive decline indistinguishable from AD. This is thought to contribute to the cognitive decline in up to 40% of elderly people over 80 years old.

Diagnosing this condition is not possible with current available investigations. The only possible way is with post-mortem brain biopsy. More recent literature has suggested that metabolic brain imaging looking at neuron glucose metabolism with particular attention to a part of the brain called the amygdala may be able to determine which patients are likely to have this protein accumulation.

We plan to analyse amygdala activity in patients that have previously had brain scans using FDG PET (Fluorodeoxy glucose, Positron Emission Tomography) and were referred with cognitive decline. Amygdala metabolic reduction in these patients will be compared to amygdala activity in the scans of cognitively normal elderly patients used as patient controls for other studies, which are available from online clinical databases.

The rates of amygdala reduction will be correlated to the presence of other causes of cognitive dysfunction as determined by their FDG PET brain scan imaging. We expect up to 40% of people referred for imaging for possible AD will have reduced amygdala metabolism, some of whom will have further scan abnormalities that suggest AD or an alternative cause of cognitive impairment. This has not been previously assessed based on a typical cohort of patients referred for assessment having various potential causes of cognitive impairment. It will also allow us to assess the rate of amygdala reduction in patients referred with cognitive impairment who have no likely cause based on their FDG PET imaging. These may represent a group of patients with TDP43 accumulation as an isolated, previously unrecognised cause for neurologic decline.

As this condition tends to occur in patients over 80 years of age, we performed a further database search of patients of age 60 to 70 years old to note differences rates of amygdala reduction in this age group.

2 Background

2.1 Definition of dementia

Dementia is a condition characterised by progressive cognitive deterioration which affects daily functionality (Chertkow, Feldman, Jacova and Massoud, 2013). The decline involves memory loss as well as other domains of cognition, such as abstract thinking, language and executive functioning, (Buffington, Lipski and Westfall, 2013). In addition, patients with dementia often experience changes in their personality, function and behaviour (Terracciano and Sutin, 2019). Due to its progressive nature, patients often do not have insight into their decline (Parrao et al., 2016).

2.1.1 Importance of dementia

Globally, dementia is the fifth-leading cause of death, accounting for 2.4 (95% CI 2.1 to 2.8) million deaths/ annum and affects approximately 50 million people (Nichols et al., 2019). The prevalence of dementia is higher in females than males, with the age-standardised global prevalence in females being 1.17- (95% CI 1.17 to 1.18) times higher than males (Nichols et al., 2019). On top of this, dementia mainly affects the older population, with a total population prevalence of 9.7% for patients over 70 in the UK and 11.2% in the US (Arapakis, Brunner, French and McCauley, 2021). The economic cost of dementia has been estimated to be 305 billion dollars in 2020 and is projected to rise to 1.5 trillion dollars in 2050 (Zissimopoulos, Crimmins and St.Clair, 2015).

2.1.2 Causes of dementia

There are multiple causes of dementia, as any condition that causes neuronal dysfunction or loss can lead to cognitive impairment. Acquired causes such as trauma (post traumatic encephalopathy), vascular (ischaemic and/or haemorrhagic stroke) and a number of primary neurodegenerative disorders (Alzheimer's, frontal lobe, Lewy body) can all contribute to the development of dementia (Duong, Patel and Chang, 2017).

These disorders can be difficult to differentiate based on clinical features. This is especially the case for early primary neurodegenerative disorders, which are classified based on their characteristic neuropathologic proteinopathy (Karantzoulis and Galvin, 2011).

Proteinopathy is defined as an excessive accumulation of a specific protein in the brain, as a result of increased production, decreased clearance and/or an altered typically phosphorylated protein conformation (Ganguly, Chakrabarti, Chatterjee and Saso, 2017).

2.1.3 Focus of dissertation

More recently, a neurodegenerative disease associated with TDP-43 proteinopathy has been defined. The disorder can have a clinical presentation indistinguishable from Alzheimer's disease. This condition is called limbic-predominant age-related TDP-43 encephalopathy (LATE) (Nelson et al., 2019). This paper will primarily focus on Alzheimer's disease and limbic-predominant age-related TDP-43 encephalopathy.

2.1.4 Definition of Alzheimer's disease

The most common cause of dementia is AD which accounts for 60-70% of all dementia cases (Reitz and Mayeux, 2014), including in patients who are 65 years of age and older (Maccioni et al., 2018). Cases that occur before the age of 65 are uncommon and account for 10 percent of all cases and are considered as early-onset AD (Guerreiro and Bras, 2015). Alzheimer's is a slowly progressing neurodegenerative disease that leads to an impairment of cognitive and behavioural functions (Breijyeh and Karaman, 2020). Currently, there is no cure for AD. However, there are treatments that can improve symptoms (Breijyeh and Karaman, 2020).

2.1.5 Causes of Alzheimer's disease

AD is associated with an accumulation of beta-amyloid plaques and neurofibrillary tangles, (Tiwari et al., 2019). Amyloid plaques and NF tangles induce microglial activation and local inflammatory responses and neurotoxicity (Tiwari et al., 2019). This results in a decrease in neurotransmission and therefore causes a reduction in cognition and memory. As the disease spreads to other parts of

the brain, more widespread and severe neuronal degeneration occurs, and memory and further multi-domain symptoms worsen (Tiwari et al., 2019). This process is sometimes referred to as AD neuropathologic change (ADNC).

AD can be considered a multifactorial disease associated with several risk factors. Factors such as genetics, age, brain injuries, vascular diseases, infections, and environmental factors (such as heavy metals) can all contribute to the development of AD (Breijyeh and Karaman, 2020). The underlying cause of amyloid-beta plaque and neurofibrillary deposition in AD is still unknown. Nonetheless, there are two main theories for the development of AD. One theory suggests that there is a change in amyloid beta-protein production and processing (A. Armstrong, 2019). The other theory suggests an impairment of cholinergic neuronal signaling is the main initiating factor of AD. Having said this, there is still no accepted theory for the pathogenesis of AD (Anand and Singh, 2013).

2.1.6 Stages of Alzheimer's disease

AD can be classified into different stages to signify the progression of the disease. These stages are presymptomatic/preclinical, mild/early AD, moderate AD, and severe/late-stage AD. Depending on the stage of the disease, the severity of symptoms may differ. In the preclinical stage, the characteristic neuropathological changes of AD in the cortex and hippocampus are present. However, there are no symptoms and no functional impairment in daily living (Dubois et al., 2016). The mild/early stage is when patients develop symptoms, predominantly impairment of memory that affect daily living. Loss of concentration, memory, changes of mood, disorientation of time and place, and depression may occur in this stage (Wattmo, Minthon and Wallin, 2016). With moderate AD, the disease has spread to the cerebral cortex areas with worsening of multi-domain symptoms. The patient will have trouble recognising family and friends. On top of this, there will be a loss of impulse control, difficulty speaking, reading, and writing (Davis et al., 2018). Finally, severe/late-stage AD involves the spread of the disease to the entire cortex, with a severe accumulation of beta-amyloid plaque and neurofibrillary tangles. This leaves the patient bedridden and completely unable to recognise even family members. The impairments cause difficulties in swallowing and urination, which consequently and frequently leads to the patient's death due to complications (Apostolova, 2016).

2.1.7 Diagnosis of AD

The standard practice of AD diagnosis varies depending on any country's given protocol. Generally, diagnosis includes a complete patient history, physical examination, cognitive screening, laboratory investigation, and brain imaging (which includes structural and functional imaging). As this dissertation focuses on FDG-PET imaging, it will only explore structural and functional imaging in depth.

2.1.8 Structural imaging

Brain imaging structural studies usually consist of radio-graphical imaging with head-computed tomography (CT) or magnetic resonance imaging (MRI) which can rule out structural causes of dementia such as tumours, normal pressure hydrocephalus, subdural hematoma, or vascular disease. In the early stages of AD, changes may not be appreciated. In later stages, pronounced changes of gyral involution in a global or asymmetric lobar distribution are present, (including hippocampal atrophy), which can support a diagnosis of AD (Hort et al., 2010; Ruan et al., 2016) or other neurodegenerative conditions. MRI demonstrates greater sensitivity compared to CT for identifying these changes (Scheltens, Fox, Barkhof and De Carli, 2002; Chetelat and Baron, 2003). Clinicians would look for disproportionate atrophy on structural MRI in the medial, basal, and lateral temporal lobes, and the medial parietal cortex for the diagnosis of AD (McKhann et al., 2011) and frontal lobes in frontotemporal dementia. Brain structural imaging is recommended at least once in the diagnosis process. Other potentially reversible causes of cerebral impairments would be excluded with laboratory testing.

2.1.9 Functional imaging

Functional imaging studies can be performed using Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) to image neuronal metabolism. FDG is a glucose analogue that is actively transported across the blood-brain barrier (Young et al., 2010) the uptake and retention of which is proportional to neuronal metabolic/synaptic activity. The location and accumulation of this agent is determined by the decay of the F^{18}isotope and the subsequent emission gamma ray picked up and

located by the imaging camera, which allows visualisation of the biochemical changes taking place (Positron Emission Tomography (PET), 2022).
Single-photon emission-computed tomography (SPECT), amyloid PET, and electroencephalogram (EEG) imaging is also used in functional imaging studies. However, it is not universally available, the most commonly used functional imaging method being FDG-PET.
FDG-PET is useful in differentiating AD-positive/negative status and can show features of reduction in regional glucose metabolic rates in patients with probate and definite AD (Mosconi et al., 2008). In patients with mild cognitive impairment FDG-PET imaging has a sensitivity of 77-89% and specificity of 74-85% in identifying AD, as compared to the post-mortem histopathologic gold standard (Vacante et al., 2013) FDG-PET has also shown to be useful in atypical presentations of AD (Suppiah, Didier and Vinjamuri, 2019).

2.2 Definition of LATE

The first recognized pathological manifestation of limbic-predominate age-related TDP-43 encephalopathy (LATE) was profound hippocampal neuron loss and gliosis, collectively termed hippocampal sclerosis. A landmark study (Dickson et al., 1994) identified 13 elderly patients who had dementia and hippocampal sclerosis, yet who lacked substantial neuropathological changes attributed to AD.

Following the detection of TDP-43 proteinopathy in frontal lobar degeneration with TDP-43 inclusions (FTLD-TDP) and in the large majority of amyotrophic lateral sclerosis (ALS) cases (Mackenzie et al., 2007), TDP-43 proteinopathy was discovered in the brains of subjects over the age of 80 without frontal lobar degeneration (FTLD) or ALS, but often with comorbid hippocampal sclerosis and/or ADNC. In retrospective studies of cognitively impaired elderly subjects, age-related TDP-43 proteinopathy has been associated with a progressive amnestic syndrome that mimicked Alzheimer's disease (Pao et al., 2011; Brenowitz et al., 2014). This occurred in the absence of severe ADNC, the prevalence of which has been shown to decrease in extreme old age (Nelson et al.,2011a, b, 2013; Brenowitz et al., 2014).

2.2.1 Importance of LATE

TDP-43 pathology is observed in 20-50% of patients with AD and in 75% of patients with severe AD (Jo et al., 2020). TDP-43 pathology is believed to begin in the amygdala, further mesial temporal structures and later spreads to the different cortex (Josephs et al., 2016). Although TDP-43 is associated with AD, recent research has shown that patients with TDP -43 can present with AD-like symptoms (such as dementia) but have no accumulation of beta-amyloid plaque in post-mortem studies (Zhang et al., 2019). Therefore, new terminologies and diagnostic criteria were created specifically for this pathology. Limbic-predominate age-related TDP-43 encephalopathy (LATE) is the recently recognized disease entity pathway to dementia, shown by previous retrospective autopsy studies. Thus, LATE was formally defined in a consensus working group report from 2019 (Nelson et al., 2019).

2.2.2 Causes of LATE

TAR DNA-binding protein 43 (TDP-43) is a protein that is encoded by the TARDBP gene, belonging to the heterogeneous nuclear ribonucleoprotein family. TDP-43 is typically located in the nucleus in healthy cells and plays a significant role in RNA regulation (Scotter, Chen and Shaw, 2015). TDP-43 is predominantly non-phosphorylated and localised mostly within the nucleus. However, in disease states, the protein is phosphorylated and often translocated to the cytoplasm (Neumann et al., 2006). The accumulation of TDP-43 (TDP-43 proteinopathy) disrupts the nuclear pore complexes and nucleocytoplasmic transport mechanisms and further accelerates aggregation, leading to neurotoxicity and dysfunction (Chou et al., 2018).

2.2.3 Features of LATE

LATE is defined as TDP-43 proteinopathy in older adults, which causes neuropathological changes (LATE-NC). LATE is mainly observed in those over 80 years of age (Nelson et al., 2019). This disease is associated with amnestic dementia, which mimics the symptoms of AD-type dementia (Nelson et al., 2011). Patients with LATE-NC tend to have comorbid brain pathologies, including amyloid-b plaques and tauopathy (McAleese et al., 2016). The difference between LATE and TDP-43 frontotemporal lobar degeneration is that LATE generally affects older subjects and has a

relatively respected neuroanatomical distribution of TDP-43 (Nelson et al., 2019). The presence of TDP-43 is associated with progressive cognitive decline. TDP-43-positive cases have more significant cognitive decline, degree of hippocampal atrophy, and hippocampal sclerosis compared to TDP-43/ADNC-negative cases (Buciuc et al., 2020). Furthermore, patients with pure LATE-NC showed slower cognitive decline than those with pure ADNC. However, those with mixed ADNC and LATE-NC, showed the fastest decline compared to either pathology alone (Kapasi et al., 2020). Currently, only post-mortem studies can be utilised to obtain a definitive diagnosis of LATE-NC, ADNC or mixed ADNC/LATE-NC.

2.2.4 Amygdala

Studies have shown progressive TDP-43 aggregates are found in the amygdala in the first stage of the disease and in the amygdala/hippocampus in the second stage (Nag et al., 2018). Studies indicate that structural changes in the amygdala volume associated with LATE-NC are beyond what can be explained by other pathological types (Makkinejad *et al.*, 2019). The amygdala area will be of particular interest in our research.

2.2.5 Diagnosis of LATE

Currently, LATE can only be diagnosed at the post-mortem setting (Buciuc et al., 2019). This process is conducted through autopsy studies focusing on neuropathologic epidemiology, where microscopic examination of the brain tissue is conducted to reveal the character of the proteins present. Antemortem brain biopsy in the ante-mortem setting can also be used to diagnose LATE status. However, this method is highly invasive and can be subject to sampling error, and thus is not often used as the risks outweigh the benefits of diagnosis.

2.2.6 Potential of FDG-PET in identifying LATE

A retrospective study of FDG-PET imaging showed differences between TDP-43-positive and negative patients. This suggests FDG-PET utility in the antemortem prediction of TDP-43 (Buciuc

et al., 2019). As neuropathologic studies have demonstrated that TDP-43 deposition first occurs in the amygdala and subsequently in the mesial temporal structures, before progressing to other brain regions, FDG metabolic activity of amygdala is likely to be the earliest and most severely reduced brain structure in TDP-43-positive patients. This has been confirmed by Buciuc et al.

2.2.7 FDG-PET scan

F-fluorodeoxyglucose (FDG) positron emission tomography (PET) alone or in-conjunction with MRI is the gold-standard imaging modality for the assessment of dementia. MRI is an imaging method that uses magnetic flux to create detailed images of tissues within the body for visualisation (MRI - Mayo Clinic, 2022). FDG is a glucose analogue that is used to image tissue glucose metabolism with insulin-dependent cellular uptake and retention through phosphorylation and is actively transported across the blood-brain barrier (Young et al., 2010). Glucose metabolism as determined by FDG uptake and retention is proportional to cellular metabolic activity in neurons, which is largely determined by their synaptic activity and the measured activity being reduced by cellular dysfunction or “drop out’/death. PET is a form of nuclear medicine that measures cells' metabolic activity, which allows visualisation of the biochemical changes taking place (Positron Emission Tomography (PET), 2022).

The European Association of Nuclear Medicine (EANM) recommends using FDG-PET in patients with cognitive decline and dementia. It can be used for early diagnosis of AD in patients with mild cognitive impairments (MCI) allowing one to see changes in synaptic activity early in the course of the disease when macro structural brain changes cannot yet be detected(Nobili et al., 2018). When MRI data are inconclusive, FDG-PET can be used to differentiate AD, vascular dementia (Marcus, Mena and Subramaniam, 2014) and distinguish between cognitive impairment of degenerative diseases from non-neurodegenerative origins, such as depression, idiopathic normal pressure hydrocephalus, and traumatic brain injury (in correlation with MRI [Guedj et al., 2021]).

2.3 Differentiating between AD and LATE

2.3.1 Clinical importance

LATE-NC is present in 40% to 50% of individuals past the age of 80 years of age (Nelson et al., 2019). The public health impact of LATE is of the same order of magnitude as Alzheimer's disease neuropathological changes (ADNC).

Comorbid ADNC and LATE-NC have become increasingly prevalent with advanced age. But the mechanisms underlying ADNC and LATE-NC have independent effects on cognitive performance (Nelson et al., 2010). Thus, it is important to distinguish between AD and LATE or combined AD and LATE which has the worse prognosis (Nelson et al., 2010). This cannot be done on clinical grounds as LATE-NC can mimic the amnestic presentations of AD (Nelson et al., 2013).

The presence of LATE-NC will also complicate the interpretation of AD-specific treatment effects that are inferred from observed cognitive outcomes. Differentiating between AD and LATE may allow improved study design, and interpretations of outcomes in AD clinical trials. A biomarker for LATE would allow better exclusion criterions to manage effects from LATE in AD trials. It will also allow for clinical trials that are directed at understanding, treating, preventing or managing LATE, by itself or with other comorbid neuro-pathologies (Nelson et al., 2019).

2.3.2 Limitations of current literature

Previous studies have shown LATE affects the amygdala but not parietal lobe metabolic activity whereas AD typically affects the parietal lobe but not the amygdala, and comorbid AD and LATE affects both.
However there has not been a study conducted on the utility of FDG-PET-assessed amygdala and parietal metabolic activity to determine LATE, AD and comorbid AD and LATE status in patients referred with cognitive decline in the antemortem setting.

3 Proposed study

The proposed study is a cross-sectional exploratory analysis, using retrospective FDG-PET data from the Western Government of Australia Department of Health and the Alzheimer's Disease Neuroimaging Initiative (ADNI) databases, to measure amygdala and parietal metabolic activity in two elderly cohorts (Cohort One [age 80y.o and above] & Cohort Two [age 60 to 70y.o]).

Subjects were categorised into three groups: the AD group, CDUA group, and the Normal (cognitively assessed normal for their age) group based on the diagnosis given at the time of FDG-PET scan, within their respective cohort.

Subjects are defined as CDUA if they are referred for FDG-PET imaging on the grounds of cognitive decline or suspicion for dementia, but do not exhibit any neurological changes which fit the requirement for any diagnosable dementia syndrome or have any other known explanation in clinical diagnosis which explains their cognitive decline status. We suspect unrecognised LATE maybe responsible for a portion of these cases.

3.1 Rational

FDG-PET can identify the level of activity in different areas of the brain (Ewers et al., 2014). We predict AD will cause a reduction in the parietal lobe but not the amygdala, LATE will only cause a reduction in the amygdala and comorbid AD/LATE will reduce both (Jacobs et al., 2012) (Cykowski et al., 2022)**.**

3.2 Objectives

At present LATE cannot be diagnosed with FDG-PET and quantitation in the ante-mortem setting looking for a hypothesised difference in amygdala and parietal lobe activity, and comorbid AD and LATE is the best that can be done.

Table 1. Predictive Hypothesis

Amygdala metabolism	Parietal lobe metabolism	Possible diagnosis
NORMAL	ABNORMAL	AD
ABNORMAL	NORMAL	LATE
	ABNORMAL	Comorbid AD and LATE

Table 1. Shows the predictive hypothesis; suspected LATE subjects would have an abnormal (defined as "below the normal range") reduction in the amygdala, but a normal reduction in the parietal lobe, whereas mixed combined comorbid AD and LATE subjects would exhibit abnormal reductions in both regions.

The normal range of metabolic activity for the amygdala and parietal areas is established by taking the mean SUVRs; these need to be determined using our Normal group. Subjects greater than two standard deviations below the normal range of metabolic activity, with an abnormal reduction only in the amygdala but not the parietal lobes will fit our hypothesised suspected LATE cases. Subjects who have a reduction in both regions below the normal range will fit our hypothesised suspected comorbid AD/LATE cases. Subjects with only had an abnormal reduction in the parietal lobe but not amygdala will fit our hypothesised pure AD cases.

We will also establish the average difference in amygdala, and parietal lobe activity between groups, (AD, CDUA vs Normal) and across age ranges (age 60 to 70 vs 80 and over) by using standard uptake value ratios (SUVRS): a quantitative method used to make regional comparison within regions of interest.

An exploratory analysis of elderly subjects may provide valuable information on the potential predictive abilities of FDG-PET using SUVRs to identify suspected LATE cases. Information from this study may point towards a direction for future research in hopes of filling the void for an ante-mortem method of identifying suspected LATE, thus enabling diagnosis earlier in the clinical pathway.

3.3 Research Question

The DPPO representation of the research question is summarised in Table 2 below.

Table 2. DPPO representation of the research question.

Design	Exploratory cross-sectional analysis
Population	Patients 60 to 70, and 80y.o and above with FDG-PET imaging and with amnestic (Alzheimer's type) dementia, or cognitively assessed Normal or CDUA
Predictor	AD or CDUA
Outcome	SUVRs

3.3.1 Primary Research Question

To determine if the prevalence of reduced measured amygdala metabolic activity in elderly cognitively impaired subjects corresponds to the predicted prevalence of pure and co-morbid LATE/ AD as suggested by neuropathologic studies.

• Subjects with abnormal amygdala, and parietal lobe SUVRs may have comorbid AD and LATE.
• Subjects with abnormal amygdala and normal parietal lobe SUVRs may have LATE.
• Subjects with abnormal parietal lobe and normal amygdala SUVRs may have AD.

3.3.2 Secondary Research Questions

1. Do the subjects with AD, or CDUA on average have more severe reduction in amygdala activity compared to normal subjects of the same age.

2. Do subjects of age 80 and up, who are cognitively assessed normal, with AD, or CDUA, on average have more sever reduction in amygdala activity compared to subjects of age 60 to 70 with the same condition.

3.3.3 Rationale

The clinical disease onset of LATE is generally with advanced age and typically seen in subject above 80y.o. LATE is uncommonly recognised in younger age groups thus we suspect to see less prevalence of amygdala reduction in the 60 to 70y.o cohort. Conversely AD progression advances

with age, which causes more prominent changes to the brain structure, with greater prevalence and severity of parietal hypometabolism in subjects over 80y.o.

Comparison across age ranges will also enable us to discover the degree of amygdala and parietal lobe reduction attributed to biological ageing or as a result of the disease in question. This will allow us to better understand amygdala and parietal lobe reduction features, to ensure we are not falsely identifying subjects with LATE, or comorbid LATE when reduction is actually attributed to biological ageing.

Most importantly, we want to see if the predictions we have for subjects with different cognitive status (AD, CDUA, Normal) can be identified, and reconfirmed in both age ranges. This will increase our confidence in FDG-PETS's utility as a predictive diagnostic method for TDP-43 LATE.

Table 3. Predictive Hypothesis

Amygdala metabolism	Parietal lobe metabolism	Possible diagnosis
NORMAL	ABNORMAL	AD
ABNORMAL	NORMAL	LATE
	ABNORMAL	Comorbid AD and LATE

Table 3. Shows the predictive hypothesis, suspected LATE subjects would have an abnormal (abnormal is defined by metabolic reduction below the Normal range) reduction in the amygdala, but parietal lobe within the normal range, whereas Mixed combined Comorbid AD/LATE would have abnormal reduction in both regions.

Predictions:
We expect to find the majority of AD cases should have a reduction in the parietal lobe but not the amygdala metabolism (characteristic feature of AD in FDG PET Brain imaging is reduction in parietal lobe metabolism [Jacobs et al., 2012]) and some cases should have a reduction in both amygdala and parietal lobe metabolism (predicted features of comorbid AD and LATE) since we know LATE is observed in 20-50% of patients with AD and in 75% of patients with severe AD (Jo et al., 2020). With regards to the CDUA subjects, the majority should have Normal amygdala and parietal lobe SUVRs. However, there may be those that show a reduction in the amygdala but no parietal lobe uptake (features of LATE). Since these patients did not meet any clinical criteria that

suggest any causes for their cognitive decline, we suspect it may be caused by LATE. We do not expect to find any cases of LATE or comorbid AD/LATE in the Normal group.

We suspect all subjects should experience amygdala and parietal lobe reduction attributed to age, and we expect to see the greatest amygdala and parietal lobe reduction in AD subject, then CDUA subjects, when compared to Normal.

The primary research question will help us determine if FDG-PET can be used in younger subjects (60 to 70y.o) to identify abnormal metabolic reduction and differentiate our hypothesised suspected LATE, pure AD and comorbid AD and LATE cases in subjects with AD, CDUA, since neurodegenerative disease have an increasing prevalence with ageing (Hugo and Ganguli, 2014). Thus, we suspect it would be more useful in subjects 80y.o and above. It would also test if our predictions for each group holds true.

The secondary research question will help us determine if there is an average reduction in amygdala and/or parietal in the AD group and the CDUA groups compared to the Normal group of the same age, the effects of different age ranges (60 to 70y.o vs. 80y.o) on average amygdala and parietal reduction in the AD, CDUA and Normal groups, and to quantify if the predicted trends hold true.

The limitation of the study is the inability to confirm that our identified LATE subjects based on amygdala activity have neuropathologic changes of LATE as confirmation. This could not be achieved even with a long-term prospective study as brain biopsy would still be required.

4 Methodology

4.1 Study Design

This has been a cross-sectional explorative analysis study which used retrospective data collected from the Government of Western Australia Department of Health(GWADH) database (national governmental archive for health records), and Alzheimer's Disease Neuroimaging Initiative (ADNI) database (AD data-sharing database for researchers globally) (ADNI | Study Design, 2022).

4.2 Study Population

4.2.1 Data source

The coverage of GWADH is only for Australian patient records, from two hospitals in Western Australia (Fiona Stanley Hospital and Sir Charles Gairdner). The GWADH database was used to search for patients referred for FDG-PET on the grounds of cognitive decline, suspicion of dementia, or received a clinical diagnosis of AD (with antemortem clinical criteria) or CDUA (subjects referred for cognitive decline or dementia, but who do not meet the clinical criteria for any diagnosable forms of dementia determined by their clinician).

We choose to use AD and CDUA subjects on the basis of the suspicion of finding cases of LATE in CDUA subjects, and cases of comorbid AD and LATE in AD patients. Since we know that in AD subjects the prevalence for comorbid AD and LATE is high, and in CDUA subjects there is no explanation for their cognitive decline, we suspect some cases may be attributed to LATE.

The ADNI database was used to search for cognitively assessed normal subjects. ADNI's cognitively assessed normal subjects were recruited from 57 sites in the United States and Canada. The cognitive assessment to deem a subject as cognitively normal for their age (ADNI | Study Design, 2022) was composed of a clinical evaluation, neuropsychological tests, genetic testing, lumbar puncture, and MRI and PET scans. The purpose of using ADNI cognitively assessed normal subjects for this study was to establish a baseline of the normal amygdala and parietal activity and a comparator group for subjects from GWADH.

4.2.2 Inclusion Criteria

1) Subject ages 60-70 years old (y.o), or 80y.o and above at the time of FDG-PET imaging.

Justification:

• The age range of 80y.o and above was chosen as there is a greater likelihood of advanced disease progression, making different dementia pathways' features easier to differentiate, thus increasing the accuracy of clinical diagnosis and consequently making our results more accurate.

• The 60-70y.o age range was chosen as a comparator to the 80y.o and above age range to see if the ROIs were influenced by age and, if so, by how much and whether it would be different depending on the group (e.g. AD, CDUA and Normal).

2) Both male and female gender.

Justification:
• Both sexes reflect the real-world population with dementia, this is so we minimise selection bias and increases generalisability of the results.

3) Received a clinical diagnosis with neurological assessment and evaluated as cognitively normal for their age (from the ADNI database).

4.2.3 Exclusion Criteria

1) Subjects who do not meet the inclusion criteria

2) Subjects with clinically diagnosed dementia other than Alzheimer's disease (e.g., frontotemporal dementia, dementia with Lewy bodies, primary progressive aphasia, corticobasal degeneration, progressive supranuclear palsy and Parkinson's disease).

Justification:
• At present this study's focus is on AD, CUDA, and Normal subjects. Thus, other clinically diagnosable dementia pathways are not within the scope of the research.

3) Patients with non-protein-pathological-related structural change or patients with primary/ secondary structural change attributed to other causes such as:

A) Patients with or who have had substance abuse (drugs/alcohol).

B) Patients with or who have had abnormal growths (cancer, leukaemia, lymphoma, lesions, malignancy [non-metastatic and metazoic]).

C) Patients with vascular-related disease (vascular dementia, prior stroke, small vessel disease, multi-infarct, infract, hypertension, cardiac history).

D) Patients with mental illness (diagnosed bipolar, schizophrenia, or depression).

E) Patients with an injury (head trauma, injury).

F) Patients with structural brain disease (infection, NPH, infection, previous HSV).

Justification:
• Substance abuse would cause structural and metabolic changes that are non-related to the research interest and would bias results.

• Abnormal growths within the brain region would cause structural changes that are non-related to the research interest and would bias results.

• Abnormal growths outside the brain region would usually result in the use of therapeutic drugs such as chemotherapy which causes structural changes within the brain and thus would be excluded to minimise confounding bias.

• Patients with non-protein-pathologies related to structural change or patients with primary or secondary structural changes attributed to exclusion criteria are not specific to the research interest and would bias the result.

4) Patients with multiple visits (only their latest and clearest scan will be included in the study)

Justification:
• Patient diagnosis is likely to be more definitive depending on disease stage, as clinical features and imaging will be more prominent. Therefore, only using the latest scan will increase the likelihood of patients being placed in the correct category to reduce bias from misclassification.

5) Subjects without complete and successful FDG-PET, and structural MRI scans of the brain.

4.3 Outcomes

4.3.1 Primary outcome

The primary outcome was the prevalence of reduced measured amygdala metabolic activity in elderly cognitive impaired subject corresponds to the predictive prevalence of pure and co-morbid TDP-43 as suggested by neuropathologic studies.

4.3.2 Secondary outcomes

The secondary outcomes:
1) The average amygdala activity in elderly subjects (80y.o and above) with AD, or CDUA compared to normal subjects of the same age.

2) The average amygdala activity in elderly subjects (80y.o and above) with AD or CDUA or Normal compared to younger(60 to 70y.o) subject of the same condition (AD, CDUA, Normal)

4.4 Ascertainment of exposure, covariates and outcomes

4.4.1 Search Strategy

We searched the GWADH database for clinical data from Fiona Stanley Hospital and Sir Charles Gairdner Hospitals from 01/01/2010 to 30/09/2021. After 2010, the model of the PET scanners remains the same. As such, this date range allows us to minimise interpretation errors. All subject scans were conducted utilising an Allegro GSO PET scanner (Philips Medical Systems). The database search was performed, using the search terms: “Alzheimer’s”, “Alzheimer,” or “cognitive" or “dementia”. The ADNI database was searched with the same date range, using the search terms: “cognitive normal”.

4.4.2 Data extraction

Data was extracted using the same search terms for two age ranges: 60 to 70, and 80y.o and above. These two age ranges were chosen to evaluate if amygdala and parietal lobe activity stayed

consistent with age and to compare prevalence of amygdala abnormality as a pathologic finding.

The imaging data of all subjects 80y.o and above meeting the inclusion criteria were included. The total number of included subjects were then subjected to the exclusion criteria. Subsequently the GWADH and ADNI databases would be searched again for ages 60 to 70y.o using the same date range and same search terms. From the search for 60 to 70y.o in the GWADH database, subjects meeting the inclusion criteria were included until GWADH Cohort One's (80y.o and above) inclusion number was matched. This is because there were more subjects in the 60 to 70y.o age range in the GWADH database. To mitigate selection bias, subjects meeting inclusion and exclusion criteria were included according to the sequential order of the search until the number of subjects was matched. The included subjects were then subjected to the exclusion criteria.

All ADNI subjects meeting the inclusion criteria were included. ADNI's inclusion number was not matched for subject 80y.o and above because we wanted a larger sample size for the Normal group. This was to increase confidence in the normal amygdala and parietal lobe ranges. Subjects from GWADH and ADNI meeting the inclusion criteria were included. The total included subjects would then be subjected to the exclusion criteria.

4.4.3 Demographic data

Demographic details were exported from the GWADH and ADNI database, which including age, gender and date of scan.

4.4.4 Data Extraction from FDG-PET imaging

All subjects' FDG-PET scans were core-registered using FMRIB Software Library v6.0 (12 dos affine transformation) to standard space templates (FreeSurfer for amygdala and parietal lobe and MCCALT for pontine) that conform to the Montreal Neurological Institute (MNI) defined standard space, to extract voxels and generate a mask for the amygdala, parietal lobe and pontine (pontine was chosen as this organ is not typically involved in the common pathways of neurodegenerative dementias). These areas formed our regions of interest (ROI).

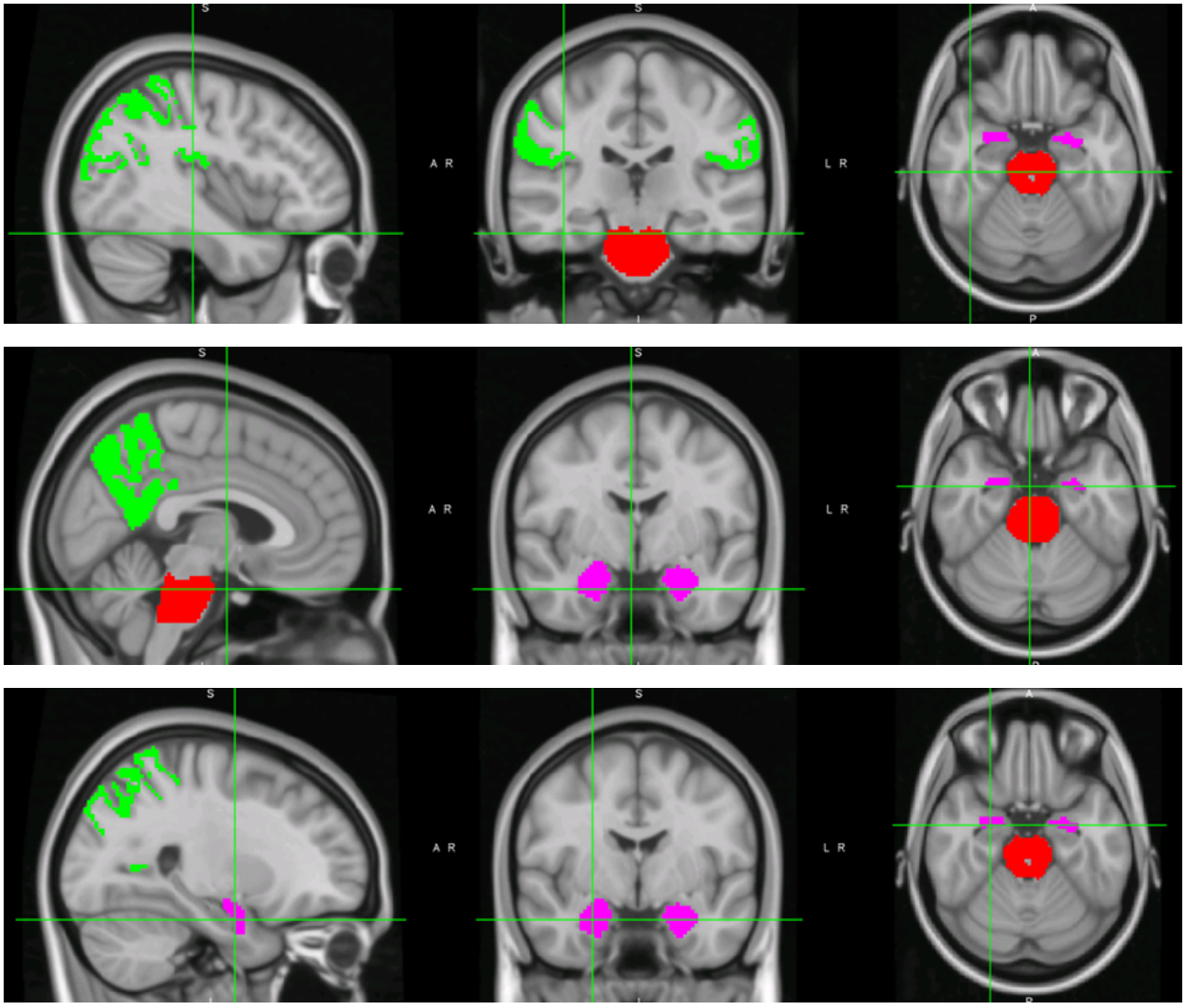


Figure 1. Regions of Interest (parietal lobe, pontine, and amygdala)

* Red = pontine *Green = parietal lobe *pink = amygdala.

Figure 1. Retrieved from FreeSurfer segmentation of subjects MRI, after co-registering to the standard space. The red highlighted area correspond to the pontine, green highlighted area corresponds to the parietal lobe and pink highlighted area corresponds to the amygdala.

4.4.4.1 Confirmation of mask accuracy with MRI images

In order to confirm the anatomic accuracy of the mask, MRI and FDG PET data of a group of 80 patients with confirmed AD were analysed, comparing the extracted brain template amygdala volumes with the actual amygdala volumes based on subjects' MRIs. Data was extracted using FreeSurfer software segmentation. Ratios were then obtained by dividing the surface area to volume. To quantify metabolic activity in the ROI, mean standard uptake value ratios (SUVRs) were used, amygdala and parietal lobe SUVRs were calculated by dividing their respective SUVR values with pontine SUVR values. The pontine region was chosen as this organ is not typically involved in neurodegenerative dementias, is anatomically well-defined allowing accurate co-registration and was the comparative region used in the previous Buciuc study.

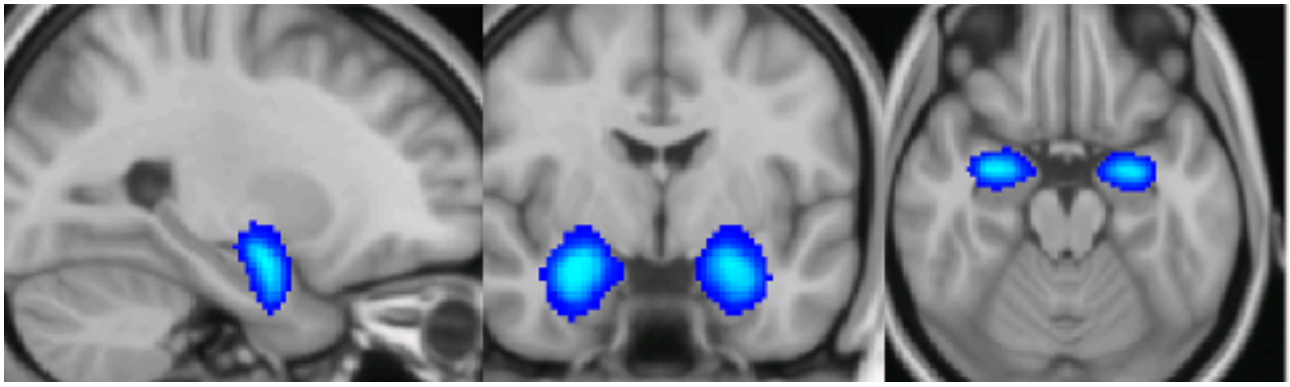


Figure 2. Group analysisAmygdala Mask (80 ADNI patients with confirmed AD)

****Blue = amygdala***

True amygdala volumes based on FreeSurfer segmentation of individual patient MRIs, after co-registering to the standard space. The highlighted blue area correspond to the amygdala, brighter blue equates to more overlap.

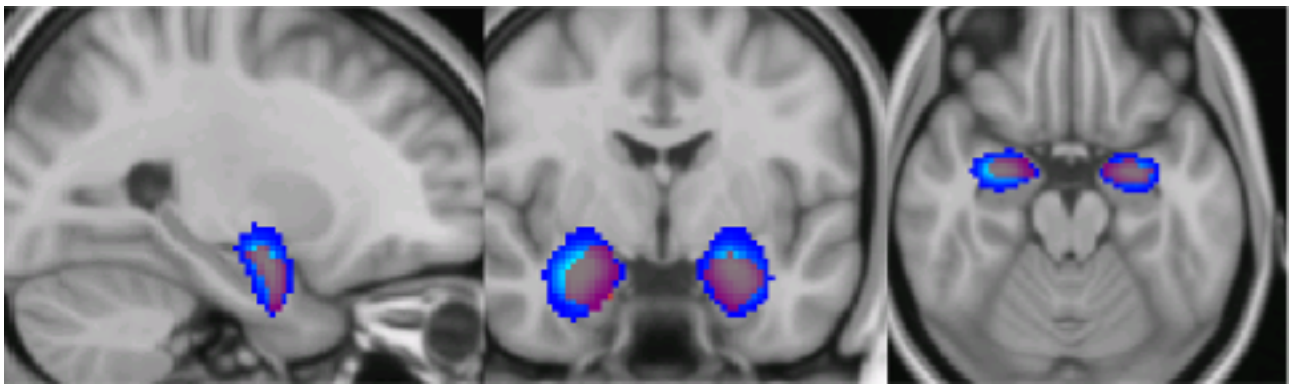


Figure 3. Extracted amygdala volumes from FDG PET emission data compared to True Amygdala volumes

Figure 3. Shows the summed up FreeSurfer segmented amygdale volumes "true volumes" (in blue) compared to the sum of the amygdala volumes as extracted from the FDG-PET emission data in the same patients' "extracted volumes" (in Red). This shows the extracted volumes corresponding well to the FreeSurfer segmented volumes "True volumes"**.**

4.5 Data management

4.5.1 Data cleaning

Due to the nature of the data extracted from the electronic health record, extensive data cleaning was required to confirm accuracy and completeness of that dataset. This included verifying units, removal of duplicate patient record and re-reviewing non-definitive diagnoses which were sent to two expert Nuclear Medicine imaging specialists for consensus review.

4.5.2 Data security

Downloaded FDG Brain PET data were analysed on a Medical Physics computer at Fiona Stanley Hospital. The subject data will remain on the picture archiving and communication system and the copied trial analysed data will remain at Fiona Stanley Hospital. The de-identified data will be stored on secure servers at Fiona Stanley Hospital for at least seven years post project completion and will be accessible only to the research team.

4.5.3 Ethical considerations

Ethics approval was obtained from the South Metropolitan Health Service Human Research Ethics Committee and is valid from 27 September 2022 to 27 September 2027 subject to compliance with the 'Conditions of Ethics Approval for a Research Project' (Appendix A). Minimal ethical considerations. De-identified group analysed data. General consent given at the time of imaging. All data generated by this study remains strictly confidential and no report containing information that would allow an individual participant in the study to be identified has been produced.

4.6 Statistical analysis

All statistical analysis were performed using Stata (Stata/BE v17.1, College Station, TX, USA). Two-sided p values <0.05 were considered statistically significant.

4.6.1 Descriptive Statistics

Descriptive statistics such as the number of subjects, mean, standard deviation, minimum, maximum, 25th percentile, median and 75th percentile, were calculated for covariates age, gender, scan year, amygdala SUVR and parietal SUVR for all subjects in their respective cohort and category (AD, CDUA, and Normal groups) and would be presented in the table of summary statistics.

4.6.2 Data Categorising

All subjects from ADNI and GWADH were separated into two cohorts by age, Cohort One included subjects 80y.o and above and Cohort two included subjects 60 to 70y.o. All subjects from the ADNI database were cognitively assessed and deemed normal for their age, and they formed our Normal groups. All subjects from GWADH were categorised into two groups (AD group, or CDUA group) and this was done by reading through subjects' clinical notes, and differentiating them by FDG PET clinical diagnoses. Subjects with an inconclusive diagnosis were sent to be reviewed by two expert FDG-PET neurologists. Patients with a diagnosis of an alternative cause for cognitive decline meeting the exclusion criteria were not included. Thus, we had three groups in each cohort (AD,

CDUA [without a clear diagnosis] and Normal).

4.6.3 Primary Outcome

The primary outcome was the prevalence of reduced measured amygdala metabolic activity in elderly cognitive impaired subject corresponds to the predictive prevalence of pure and co-morbid TDP-43 as suggested by neuropathologic studies.

LATE causes an abnormal reduction in the amygdala and later further structures with sparing of the parietal lobe. Current literature indicates isolated AD-NC causes a reduction to the parietal lobe soon after precuneal and posterior cingulate reduction with sparing of the amygdala. An unknown but likely significant portion of patients have a comorbid pathology with AD and LATE changes leading to a reduction in both amygdala and parietal lobes.

Thus, we wanted to see if we could identify subjects which fit the predictions of each disease in our group of elderly patients referred with cognitive decline and potential AD. This may allow us to differentiate LATE from AD, and comorbid AD and LATE in an ante-mortum setting, with a mixed clinical presentation. Therefore, we developed this predictive hypothesis which summarises the predictions.

Table 4. Predictive Hypothesis

Amygdala metabolism	Parietal lobe metabolism	Possible diagnosis
NORMAL	ABNORMAL	AD
ABNORMAL	NORMAL	LATE
	ABNORMAL	Comorbid AD and LATE

Table 4. Shows the predictive hypothesis, suspected LATE subjects would have an abnormal (abnormal is defined by metabolic reduction below the normal range) reduction in the amygdala, but the parietal lobe within the normal range, whereas combined comorbid AD and LATE would have an abnormal reduction in both regions.

To find abnormal reduction we needed to work out what the normal range of metabolic activity for amygdala and parietal lobes were for our two cohorts. As a number of parameters can affect the

measured activity from an ROI (region of interest) including administered activity, time for administration to imaging (isotope decay time) and the number of camera-specific parameters, standardised uptake values ratios (SUVRs) have been derived. This takes some of these factors into account for an individual scan. More accurate internal quantitation in a specific condition requires SUVR, comparing the brain region of interest in a clinical condition with an area of the brain which is unlikely to be affected. As demonstrated in the Mask analysis, data extraction section, we used the pons as our normal reference region.

To quantify metabolic activity amygdala SUVRs and parietal SUVRs and were calculated by dividing the amygdala SUVR (please view above data extraction for how ratios were extracted from FDG-PET scans) by the pontine and the parietal SUVRs were calculated by dividing the parietal ratio by the pontine ratio as well. The pontine was chosen as this organ is not typically involved in the common pathways of neurodegenerative dementias.

We used the normal groups in each cohort to generate an SUVR cut-off threshold, being mean amygdala/pontine SUVR – 2SD and parietal/pontine SUVR -2SD. The normal range (the estimate of mean ± 2 SD assumes an approximate normal distribution, normal distribution for normal groups was checked with histograms). Each subject's SUVRs were then compared to our Normal range. Subjects with a reduction below the normal range were identified and labelled depending on which disease category they fitted.

We used two cohorts to determine if FDG-PET with quantitation of the amygdala and parietal lobe, can identify an abnormal reduction in amygdala in the younger cohort which may represent a preclinical process.

4.6.4 Secondary Outcomes

Secondary Outcome One:

*The average amygdala activity in elderly subjects (80*y.o *and above) with AD, or CDUA compared to normal subjects of the same age.*

Boxplots of SUVRs in different groups were plotted. Linear regression was done to estimate differences in amygdala or parietal lobe SUVR between groups. We performed unadjusted linear regression and adjusted regression for potential confounders (age, gender and date of scan). Normality of residual distributions were checked using quantile-quantile plots, histograms and scatter plots.

We made the following comparisons of amygdala and parietal activity between:
CDUA and AD groups in Cohort One compared to the Normal group in Cohort One.
CDUA and AD groups in Cohort Two compared to the Normal group in Cohort Two.

Justification:
The objective is to establish if there were any group effects. This lets us determine whether or not AD subjects on average exhibit a greater reduction in the parietal lobe compared to Normal (which fits AD proteinopathology), or exhibit a reduction in both the amygdala and the parietal lobe (which fits comorbid AD and LATE proteinopathology). This also lets us determine whether or not CDUA subjects exhibit a greater reduction in the amygdala and a lesser one in the parietal lobe (which fits with LATE pathology), which is of interest because we don't know what is causing these subjects to experience cognitive decline, and it could potentially be attributed to LATE.
It is to identify such trends in each group that we did linear regressions comparing both the CDUA and AD groups to the Normal group. We used two cohorts, Cohort One was comprised of subjects of age 80 and over, while Cohort Two was comprised of subjects of age 60 to 70, to determine if predictions hold in both cohorts.

Secondary Outcome Two:
*The average amygdala activity in elderly subject (80*y.o *and above) with AD or CDUA or Normal compared to younger(60 to 70*y.o*) subject of the same condition (AD, CDUA, Normal)*

Boxplots of SUVRs in different groups were plotted. Linear regression was done to estimate differences in amygdala or parietal lobe SUVR across Cohorts One and Two, within the same cognitive statu group. We did an unadjusted linear regression and adjusted linear regression for potential confounders (age, gender and date of scan). Normality of residual distributions were checked using quantile-quantile plots, histograms and scatter plots.

We made the following comparisons of amygdala and parietal activity between:

- Cohort One's CDUA group amd Cohort Two's CDUA group – some of the elderly patients in Cohort One with cognitive decline will have LATE. Amygdala reduction is less likely and, if present, less severe in this age group.

- Cohort One's AD group and Cohort Two's AD group – while young onset AD < 65yo is infrequent there may be marked cortical metabolic changes. This group should have less amygdala reduction due to LATE, as this is primarily a disease of the elderly.

- Cohort One's Normal group compared to Cohort Two's Normal group – we hypothesize that amygdala activity in cognitively normal elderly subjects (Cohort 1, > 80yo+) may be lower than amygdala activity in a group of younger subjects (Cohort 2, 60 -70 yo).

Justification:
This is so we could establish whether there is an average difference in SUVR between ages for the same dementia category, and Normal categories, which will then help us understand whether or not our ROI SUVRs remains constant with age and fit the expected changes based on our understanding of LATE.

5 Results

5.1 Data acquisition & search Results

5.1.1 Details of included data

From the search we included all subjects meeting Cohort One's (80y.o and above) inclusion criteria: 272 subjects from GWADH, and 83 subjects from ADNI were included. A total of 355 subjects were then subjugated to the exclusion criteria. In Cohort Two's (60-70y.o) 272 subjects from GWADH and 58 subject from ADNI met the inclusion criteria and were included. A total of 330 subjects were then subjected to the exclusion criteria.

The search results for cohort one and two are summarised in the flow diagrams *(Figure 4 and 5)*.

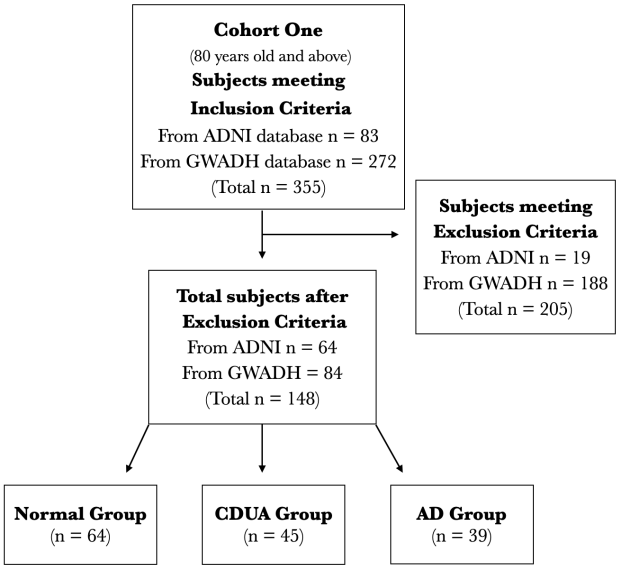


Figure 4. Age 80 and above

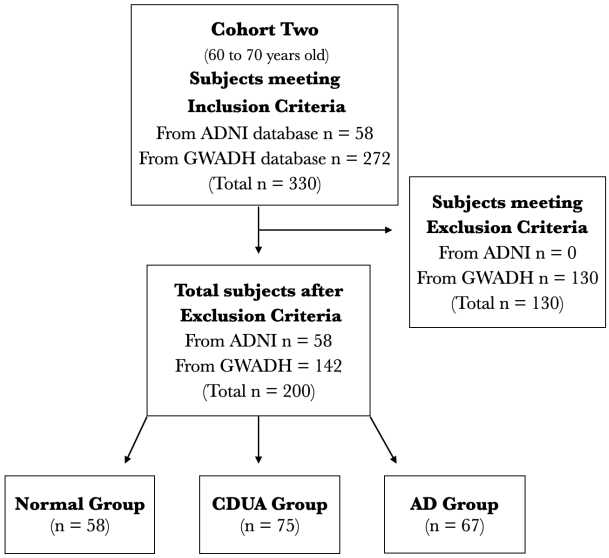


Figure 5. Age 60 to 70

Results show that after removal of duplicates and screening of full text versions of clinical notes, scans and subjugation against the exclusion criteria, 205 subjects were ineligible and excluded from Cohort One (80 years old and above) and 130 were excluded from Cohort Two (60 to 70 years old). For Cohort One a total of 148 subjects were identified as eligible for the study. Out of these subjects, 39 subjects were categorised into the AD group, 45 subjects into the CDUA group, and 64 subjects into the Normal group.

For Cohort Two a total of 200 subjects were identified as eligible for the study, and out of these, 67 subjects were categorised into the AD group, 75 subjects into the CDUA group, and 58 subjects into the Normal group.

5.1.2 Details of excluded data

Table 5. Cohort One details exclusion

**N = Number*

Parkinson's	Vascular	Abnormal Growth	Injury & structural brain disease	Mentally Ill	Substance Induced	Scan Issues	Other Neurological dementia
N = 13	N = 20	N = 28	N = 6	N = 10	N = 3	N = 42 N= 19 (ADNI)	N = 66

In cohort One, out of 355 subjects, 188 subjects from GWADH were excluded after assessment of their full clinical notes and scan, which indicated they either did not meet the eligibility criteria, or met an exclusion criteria.

In 44 cases the clinical diagnosis was not clear, and the images were reviewed blind to the clinical history, with the scan classified based on a consensus report by two expert FDG PET neuroimaging specialists. 13 were excluded for Parkinson's disease. 10 were excluded for depression and mental illness. 28 were excluded for cancer and other malignancies. 20 were excluded for vascular reasons. 6 were excluded for injury and structural brain disease. 3 were excluded for substance abuse. 42 were excluded for a missing scan or scan quality issues. 66 were excluded for other neurological dementia reasons. 19 subjects met the exclusion criteria for scan issues from the ADNI database.

Table 6. Cohort Two details of exclusion

** N = number*

Parkinson's	Vascular	Abnormal Growth	Injury & structural brain disease	Mentally Ill	Substance Induced	Scan Issues	Other Neurological dementia	Multiple Entries
N = 11	N = 6	N = 9	N = 3	N = 10	N = 4	N = 12	N = 39	N = 36

In Cohort Two, out of 330 subjects, 130 subjects from GWADH were excluded after assessment of their full clinical notes, or a scan indicated that they either did not meet the eligibility criteria, or met the exclusion criteria. In 31 cases, the clinical diagnosis was not clear and the images were reviewed blind to the clinical history with the scan classified based on a consensus report by two expert FDG PET neuroimaging specialists. 11 were excluded for Parkinson's disease. 10 were excluded for depression and mental illness. 9 were excluded for cancer and other malignancies. 6 were excluded for vascular reasons. 3 were excluded for injury and structural brain disease. 4 were excluded for substance abuse. 12 were excluded for a missing scan or scan quality issues. 39 were excluded for other neurological dementia reasons, and 36 were excluded for multiple entries. No subjects met the exclusion criteria from the ADNI database.

5.2 Summary statistics

5.2.1 Summary statistic for cohort one

Table 7. Table of Summary Statistics for Cohort One (80y.o and above)

**statistics present for gender was number of males and percentage * N = Number, * SD = Standard deviation, *Min = Minimum, *Max = Maximum*

AD Group								
Covariate	**N**	**Mean**	**SD**	**Min**	**Max**	**25th Percentile**	**Median**	**75th Percentile**
Age	39	83	2.60	80	91	81	82	85
Gender Male (%)	39	27 (69.2%)	-	-	-	-	-	-
Scan Year	39	2017	2.70	2012	2021	2015	2018	2019
Amygdala SUVR	39	1.04	0.31	0.58	1.98	0.81	0.95	1.26
Parietal lobe SUVR	39	1.27	0.15	1.02	1.60	1.16	1.23	1.34
CDUA Group								
Age	45	83	2.5	80	89	81	83	85
Gender M (%)	45	26 (57.8%)	-	-	-	-	-	-
Scan Year	45	2017	2.50	2011	2021	2016	2017	2019
Amygdala SUVR	45	1.04	0.11	0.78	1.32	0.97	1.05	1.12
Parietal lobe SUVR	45	1.42	0.13	1.21	1.82	1.32	1.43	1.49
NORMAL Group								
Age	64	83	2.33	80	89	81	83	85
Gender M (%)	64	40 (62.5%)	-	-	-	-	-	-
Scan Year	64	2011	1.77	2010	2018	2011	2011	2012
Amygdala SUVR	64	1.07	0.08	0.88	1.25	1.02	1.07	1.13
Parietal lobe SUVR	64	1.50	0.13	1.18	1.79	1.40	1.47	1.59

Table 7 presents the summary statistics of Cohort One. Number of subjects, Mean, Standard Deviation, Min, Max, 25th Percentile, Median and 75th Percentile for the Covariates Age, Gender, Scan Year, Amygdala SUVR. For Groups AD, CDUA and Normal.

The AD group contained 39 subjects, and the CDUA group contained 45 subjects. The percentage of males in the normal group was 62.5%. This was slightly higher in the AD group at 69.2%, but slightly lower in the CDUA group at 57.8%. There were 64 subjects in the Normal group, 100% of these came from the ADNI database.

The Cohort One mean amygdala SUVR in the Normal group was 1.07. It was slightly lower in the CDUA group at 1.04 and the AD group at 1.04. The parietal lobe SUVR in the Normal group was

1.50. It was slightly lower in the CDUA group at 1.42 and much lower in AD group at 1.27.

5.2.2 Summary statistics for cohort two

Table 8. Summary Statistics for Cohort Two (60 to 70y.o)

**statistics present for gender was number of male and percentage * N = Number, * SD = Standard deviation, *Min = Minimum, *Max = Maximum*

AD								
Covariate	**Number**	**Mean**	**SD**	**Min**	**Max**	**25th Percentile**	**Median**	**75th Percentile**
Age	67	65.76	3.17	60	70	63	66	69
Gender Male (%)	67	34 (50.74%)	-	-	-	-	-	-
Scan Year	67	2016	2.95	2010	2021	2015	2017	2019
Amygdala SUVR	67	1.01	0.12	0.54	1.27	0.96	1.02	1.09
Parietal lobe SUVR	67	1.26	0.16	0.95	1.61	1.15	1.24	1.35
CDUA								
Age	75	65.75	3.15	60	70	63	67	69
Gender Male (%)	75	43 (57.33%)	-	-	-	-	-	-
Scan Year	75	2016	2.70	2011	2021	2015	2017	2019
Amygdala SUVR	75	1.09	0.09	0.85	1.43	1.04	1.10	1.14
Parietal lobe SUVR	75	1.57	0.15	1.11	1.87	1.47	1.58	1.68
NORMAL								
Age	58	67.38	2.82	62	70	66	67	69
Gender M (%)	58	21 (36.21%)	-	-	-	-	-	-
Scan Year	58	2013	1.98	2010	2019	2012	2012	2014
Amygdala SUVR	58	1.12	0.08	0.98	1.34	1.05	1.11	1.18
Parietal lobe SUVR	58	1.63	0.15	1.33	2.18	1.55	1.62	1.72

Table 8. presents the summary statistics of Cohort Two. Number of subjects, Mean, Standard Deviation, Min, Max, 25th Percentile, Median and 75th Percentile for the Covariates Age, Gender, Scan Year, Amygdala SUVR for Groups AD, CDUA and Normal.

The AD group contained 67 subjects, and the CDUA group contained 75 subjects The percentage of males in the Normal group was 36.2%. This was slightly higher in the AD group at 50.7% and slightly higher in the CDUA group at 57.3%.

The Cohort2, mean amygdala SUVR in the Normal group was 1.12. It was slightly lower in the CDUA group at 1.09 and the AD group at 1.01. The parietal SUVR in the normal group was 1.63. It was slightly lower in the CDUA group at 1.57 and much lower in the AD group at 1.26. There were 58 subjects in the Normal group, 100% of these came from the ADNI database.

5.3 Normal SUVR range of amygdala and parietal lobe

For identification of subjects below the normal range

Table 9. Cohort One & Two Normal Ranges

** SD = Standard Deviation * Min = Minimum * Max = Maximum*

Cohort One				
Normal Group	Number of cases	Mean (95%CI)	SD	Normal Range Min to Max =(mean ±[SD x 2])
Amygdala SUVR	64	1.068 (95%CI 1.047 to 1.088)	0.08	0.908 to 1.228
Parietal lobe SUVR	64	1.498(95%CI 1.466 to 1.530)	0.13	1.238 to 1.758
Cohort Two				
Amygdala SUVR	58	1.116 (95%CI 1.091 to 1.137)	0.080	0.956 to 1.276
Parietal lobe SUVR	58	1.633 (95%CI 1.592 to 1.673)	0.154	1.325 to 1.941

Table 9. shows that for normal subjects of Cohort One, the range for amygdala SUVR was 0.908 to 1.228 and parietal SUVR 1.238 to 1.758. For normal subjects of Cohort Two, the range for amygdala SUVR was 0.956 to 1.276 and parietal SUVR1.325 to 1.941. Normal range was calculated by taking the mean ± 2 standard deviation.

Equation: (mean ± [SDx2]) = Normal Range

Based on the above, the cutoff threshold for abnormally reduced amygdala activity for Cohort One and Two are SUVR 0.908 and SUVR 0.956 respectively. The cutoff threshold for abnormally reduced parietal activity is for Cohort One and Two are SUVR 1.238 and SUVR 1.325 respectively.

5.3.1 Subjects with amygdala/parietal lobe SUVR below the normal range

Table 10. Cases with Amygdala and/or Parietal Lobe SUVR Below the Normal Range

Cohort One							
Normal Range Amygdala SUVR = 0.908 to 1.228 Normal Range Parietal Lobe SUVR = 1.238 to 1.758							
Groups	Subjects n	Mean (95% CI)	Amygdala SUVR below normal range and parietal lobe SUVR within the normal range n (%)	Parietal lobe SUVR below normal range n (%)	Amygdala SUVR within normal range and parietal lobe below normal range n (%)	Amygdala SUVR below normal range n (%)	Both amygdala SUVR and parietal lobe SUVR below normal range n (%)
CDUA	45	Amygdala SUVR = 1.037 (95%CI 1.004 to 1.070) Parietal lobe SUVR = 1.421 (95%CI 1.383 to 1.460)	4 (8.889%)	4 (8.889%)	3 (6.667%)	5 (11.112%)	1 (2.222%)
AD	39	Amygdala SUVR = 1.038 (95%CI 0.938 to 1.139) Parietal lobe SUVR = 1.267 (95%CI 1.220 to 1.314)	2 (5.130%)	22 (56.410%)	18 (46.154%)	7 (17.950%)	5 (12.820%)
Normal	64	Amygdala SUVR = 1.068 (95%CI 1.047 to 1.088) Parietal lobe SUVR = 1.498 (95%CI 1.466 to 1.530)	2 (3.125%)	0 (0.000%)	0 (0.000%)	2 (3.125%)	0 (0.000%)
Cohort Two							
Normal Range Amygdala SUVR = 0.956 to 1.276 Normal Range Parietal Lobe SUVR = 1.325 to 1.941							
CDUA	75	Amygdala SUVR = 1.092 (95%CI 1.071 to 1.113) Parietal SUVR = 1.575 (95%CI 1.540 to 1.610)	2 (2.670%)	5 (6.667%)	5 (6.667%)	2 (2.670%)	0 (0.000%)
AD	67	Amygdala SUVR = 1.013 (95%CI 0.983 to 1.042) Parietal SUVR = 1.256 (95%CI 1.217 to 1.294)	7 (10.450%)	44 (65.672%)	35 (52.239%)	16 (23.880%)	9 (13.433%)
Normal	58	Amygdala SUVR = 1.116 (95%CI 1.091 to 1.137) Parietal SUVR = 1.633 (95%CI 1.592 to 1.673)	0 (0.000%)	0 (0.000%)	0 (0.000%)	0 (0.000%)	0 (0.000%)

**95%CI = 95 percent confidence internal *n = number*

Table 10. Shows the number of subjects in groups CDUA, AD and Normal, of Cohort One and Two, the mean and 95 percent confidence internals for amygdala and parietal lobe SUVR, and the number and percentage of subjects with amygdala and/or parietal lobe SUVR below the normal range.

In Cohort One's CDUA group, 5 (11.11%) of the subjects had amygdala SUVR below the normal range and 4 (8.89%) subjects had parietal SUVR below the normal range. 3 (6.667%) had amygdala SUVR within normal range and parietal SUVR below normal range. 4 (8.89%) of subjects had amygdala SUVR below the normal range and parietal lobe SUVR within normal range. 1 (2.22%) had both amygdala and parietal SUVR below normal range. In Cohort One's AD group, 7 (17.95%)

subjects had amygdala SUVR below normal range and 22 (56.41%) subjects had parietal lobe SUVR below normal range.18 (46.154%) had amygdala SUVR within normal range and parietal lobe SUVR below normal range. 2 (5.13%) subjects had amygdala SUVR below normal range and parietal lobe SUVR within normal range. 5 (12.820%) subjects had both amygdala and parietal lobe SUVR below normal range. In Cohort One's Normal group, 2 (3.125%) subjects had amygdala SUVR below normal range and parietal SUVR within the normal range.

In Cohort Two's CDUA group, 2 (2.67%) subjects had amygdala SUVR below normal range, and 5 (6.67%) of subjects had parietal lobe SUVR below normal range. 5 (6.67%) subjects had amygdala SUVR within normal range and parietal lobe SUVR below normal range. 2 (2.67%) subjects had amygdala SUVR below normal range, and parietal lobe SUVR within normal range. No subjects had both amygdala and parietal lobe SUVR below normal. In Cohort Two's AD group, 16 (23.88%) subjects had amygdala SUVR below normal range, and 44 (65.67%) subjects had parietal lobe SUVR below normal range. 35 (52.24%) subjects had amygdala within normal range, and parietal lobe SUVR below normal range. 7 (10.45%) subjects had amygdala SUVR below normal range, and parietal lobe SUVR within normal range. 9 (13.43%) subjects had both amygdala and parietal SUVR below normal range. In Cohort Two's Normal group, no subjects had amygdala or parietal lobe SUVR below normal range.

5.3.2 Subjects with features of AD, LATE and comorbid AD/LATE

Table 11. Cases with Suspected, pure AD, pure LATE and, Comorbid AD/LATE

**LATE = Abnormal Amygdala Reduction & Normal Parietal Lobe*
**Comorbid AD and LATE = Abnormal Amygdala Reduction & Abnormal Lobe Parietal Reduction*
** AD = Abnormal Parietal Lobe & Normal Amygdala*

	Cohort One (Over 80 years old)			Cohort Two (60 -70 years old)		
	AD	LATE	Comorbid AD & LATE	AD	LATE	Comorbid AD & LATE
CDUA	3 (6.667%)	4 (8.889%)	1 (2.222%)	5 (6.667%)	2 (2.670%)	0 (0.000%)
AD	18 (46.154%)	2 (5.130%)	5 (12.820%)	35 (52.240%)	7 (10.450%)	9 (13.433%)
Normal	0 (0.000%)	2 (3.125%)	0 (0.000%)	0 (0.000%)	0 (0.000%)	0 (0.000%)

Table 11. shows the proportion of subjects which conform to the predictive hypothesis.

In Cohort One's CDUA group, 3 (6.67%) subjects have suspected AD, 4 (8.89%) subjects have suspected LATE and 1 (2.22%) has suspected comorbid AD and LATE. In Cohort One's AD group, 18 (46.15%) have suspected AD, 2 (5.13%) subjects have suspected LATE and 4 (10.26%) subjects has suspected comorbid AD and LATE. In Cohort One's Normal group 2 (3.13%) has suspected LATE.

In Cohort Two's CDUA group, 5 subject have suspected AD, 2 (2.67%) subjects have suspected LATE and no subjects have suspected comorbid AD and LATE. In Cohort Two's AD group, 35 (52.24%) subjects have suspected AD, 7 (10.45%) subjects have suspected LATE, and 9 (13.43%) subjects have suspected comorbid AD and LATE. In Cohort Two's Normal group, no subject complies with the predictive hypothesis.

5.4 Secondary results linear regression:

Differences in Amygdala/Parietal lobe SUVR Between Groups & Across Cohorts for the Same Group

5.4.1 CDUA group

Table 12. Linear Regression Results for the comparison between CDUA groups vs Normal in Cohort One and Two, and the results for CDUA in Cohort One vs CDUA in Cohort Two.

** adjusted for: age, gender, dos *95% CI = 95% confidence interval*

Linear Regression		
Variable, Mean (95%CI)	**Coefficient (95% CI)**	**p-value**
Cohort One (Ages 80 and Above) Normal vs. CDUA		
Unadjusted Analysis		
Amygdala SUVR (Normal vs. CDUA), 1.068 (95%CI 1.047 to 1.088) vs. 1.037 (95%CI 1.004 to 1.070)	0.031 (95%CI -0.006 to 0.068)	0.096
Adjusted Analysis		
Amygdala SUVR	0.055 (95%CI -0.002 to 0.111)	0.059
Unadjusted Analysis		
Parietal lobe SUVR (Normal vs. CDUA), 1.498(95%CI 1.466 to 1.530) vs. 1.421(95%CI 1.383 to 1.460)	0.077(95%CI 0.0279 to 0.126)	0.002
Adjusted Analysis		
Parietal lobe SUVR	0.132(95%CI 0.052 to 0.211)	0.001
Cohort Two (Ages 60-70) Normal vs CDUA		
Unadjusted Analysis		
Amygdala SUVR (Normal vs. CDUA), 1.116 (95%CI 1.095 to 1.137) vs. 1.092 (95%CI 1.071 to 1.113)	0.024 (95%CI -0.006 to 0.054)	0.111
Adjusted Analysis		
Amygdala SUVR	0.041 (95% CI 0.002 to 0.079)	0.038
Unadjusted Analysis		
Parietal lobe SUVR (Normal vs. CDUA), 1.633 (95%CI 1.592 to 1.673) vs. 1.575 (95%CI 1.540 to 1.610)	0.577 (95%CI 0.005 to 0.111)	0.034
Adjusted Analysis		
Parietal lobe SUVR	0.048 (95%CI-0.021 to 0.117)	0.168
Cohort One (Ages 80 and Above) CDUA vs. Cohort Two (Ages 60-70) CDUA		
Unadjusted Analysis		
Amygdala SUVR (CDUA 80+ vs CDUA 60-70), 1.037 (95%CI 1.004 to 1.070) vs 1.092 (95%CI 1.071 to 1.113)	-0.055 (95%CI-0.091 to -0.018)	<0.005
Adjusted Analysis		
Amygdala SUVR	0.064 (95%CI -0.046 to 0.174)	0.254
Unadjusted Analysis		

Parietal lobe SUVR (CDUA 80+ vs CDUA 60-70), 1.421 (95%CI 1.383 to 1.459) vs. 1.575 (95%CI 1.540 to 1.610)	-0.154 (95%CI -0.208 to -0.100)	<0.001
Adjusted Analysis		
Parietal SUVR	-0.061(95%CI -0.227 to 0.106)	0.472

5.4.2 *The comparisons between cohort One (80y.o+) CDUA group vs normal group*

For subjects in Cohort One, the mean amygdala SUVR was larger in the Normal group 1.068 (95%CI 1.047 to 1.088) compared to the CDUA group 1.037 (95%CI 1.004 to 1.070). There was no evidence of a difference in amygdala SUVR between these group before 0.031 (95%CI -0.006 to 0.068, p=0.096) or after adjusting for confounding 0.055 (95%CI -0.002 to 0.111, p=0.059). In contrast, there was a difference in parietal lobe SUVR between these groups before and after adjusting for confounding. The mean parietal lobe SUVR was 1.498(95%CI 1.466 to 1.530) in the Normal group compared to the CDUA group's 1.421 (95%CI 1.383 to 1.460), difference before adjustment 0.077(95%CI 0.0279 to 0.126, p=0.002) and difference after adjusting 0.132(95%CI 0.052 to 0.211, p=0.001). The following box plot show CohortOne's CDUA group amygdala and parietal lobe SUVR compared to the Normal group and histograms for normal distribution.

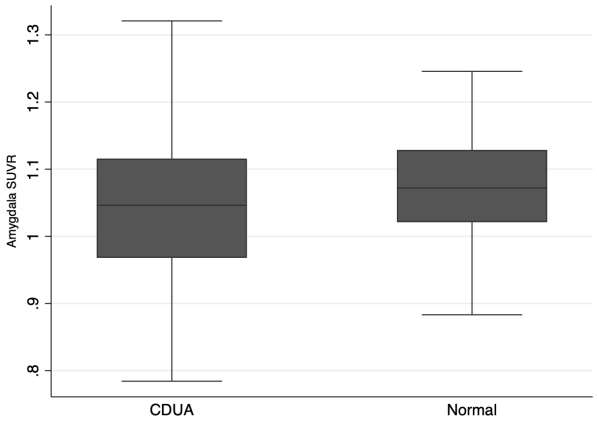


Figure 6. Box plot of Cohort One's CDUA group's amygdala SUVR compared to the Normal group

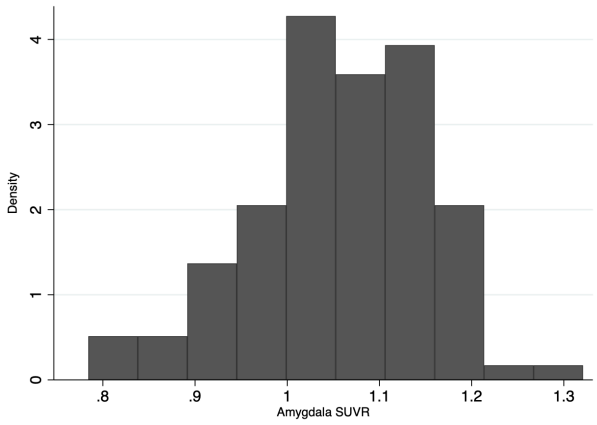


Figure 7. Histogram of Cohort One's CDUA group's amygdala SUVR compared to the Normal group

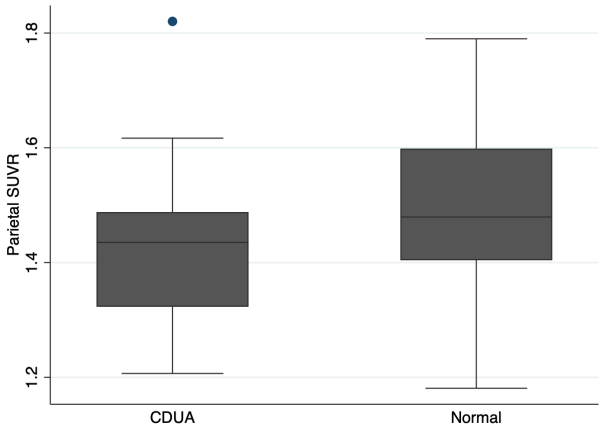


Figure 8. Box plot of Cohort One's CDUA group's parietal lobe SUVR compared to the Normal group

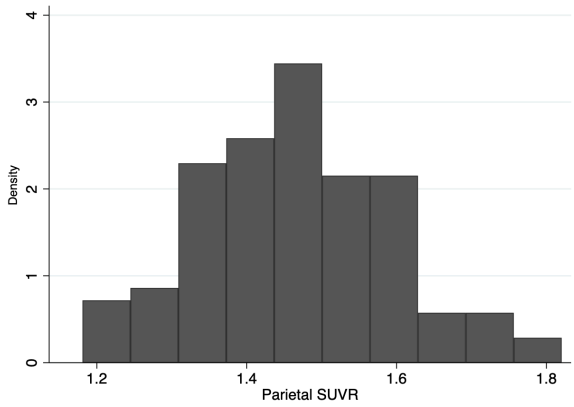


Figure 9. Histogram Cohort One's CDUA group's Parietal lobe SUVR compared to the Normal group

5.4.3 *The comparisons between cohort two (60-70y.o) CDUA group vs normal group*

For subjects in Cohort Two, the mean amygdala SUVR was larger in the Normal group 1.116 (95%CI 1.095 to 1.137) compared to the CDUA group 1.092 (95%CI 1.071 to 1.113). There was no evidence of a difference in amygdala SUVR between these groups before 0.024 (95%CI -0.006 to 0.054, p = 0.111) adjusting for confounding but there was a difference after 0.041 (95% CI 0.002 to 0.079, p = 0.038). In contrast there was a difference in parietal lobe SUVR between these groups before but not after adjusting for confounding. The mean parietal SUVR was larger in the Normal group 1.633 (95%CI 1.592 to 1.673) compared to the CDUA group 1.575 (95%CI 1.540 to 1.610), difference before adjustment 0.577 (95%CI 0.005 to 0.111, p = 0.034) and after adjusting 0.048 (95%CI-0.021 to 0.117, p = 0.168). The following box plot show Cohort Two's CDUA group amygdala and parietal lobe SUVR compared to the Normal group and histograms for normal distribution.

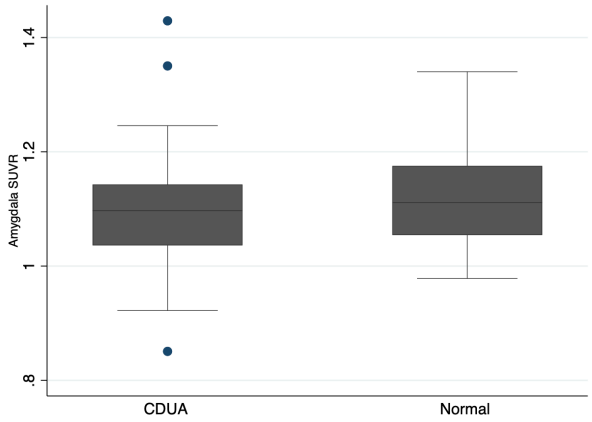


Figure 10. Box plot of Cohort Two's CDUA group's amygdala SUVR compared to Normal group

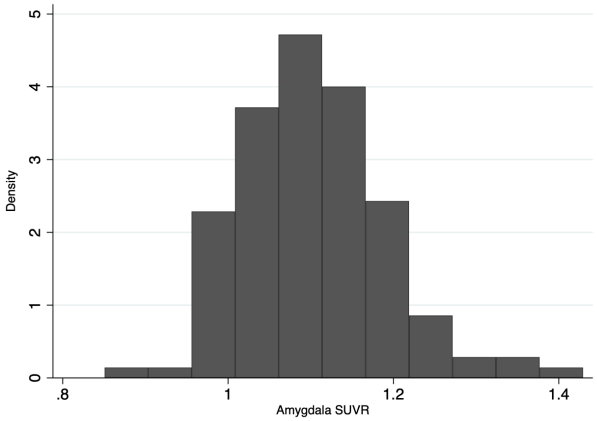


Figure 11. Histogram of Cohort Two's CDUA group's amygdala SUVR compared to Normal group

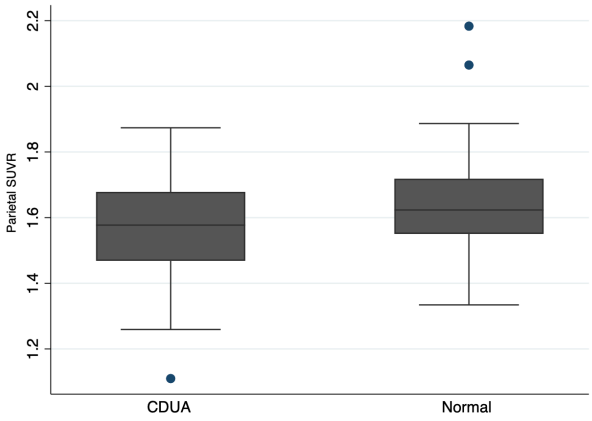


Figure 12. Box plot of Cohort Two's CDUA group's parietal SUVR compared to Normal group

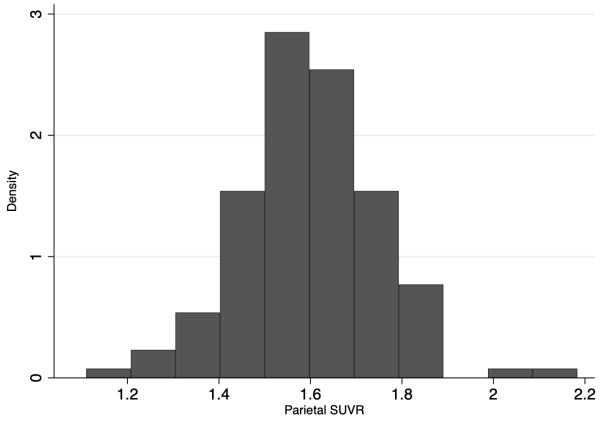


Figure 13.Histogram Cohort Two's CDUA group's parietal SUVR compared to Normal group

5.4.4 *The comparison of cohort one's CDUA group vs. cohort two's CDUA group*

Between Cohorts One and Two's CDUA groups, the mean amygdala SUVR was smaller in Cohort One 1.037 (95%CI 1.004 to 1.070) compared to Cohort Two 1.092 (95%CI 1.071 to 1.113). There was a difference in amygdala SUVR between these groups before 0.055 (95%CI-0.091 to -0.018, p=<0.005) but not after adjusting for confounding 0.064 (95%CI -0.046 to 0.174, p=0.254). There was also a difference in parietal lobe SUVR between these groups before but not after adjusting for confounding. The mean parietal SUVR was 1.421 (95%CI 1.383 to 1.459) in the Cohort One CDUA group compared to the Cohort Two CDUA group 1.575 (95%CI 1.540 to 1.610), difference before adjustment 0.154 (95%CI -0.208 to -0.100, p=<0.001) and difference after adjusting 0.061(95%CI -0.227 to 0.106, p=0.472). The following box plot show Cohort One's CDUA group amygdala and parietal lobe SUVR compared to Cohort Two's and histograms for normal distribution.

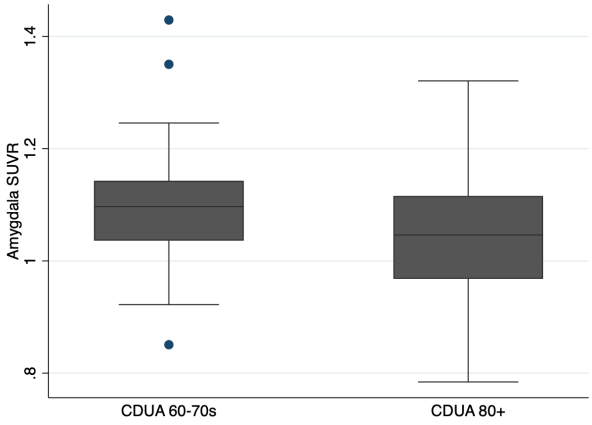


Figure 14. Box plot of across Cohort comparison of the amygdala SUVR between the CDUA group in Cohort One vs the CDUA group in Cohort Two

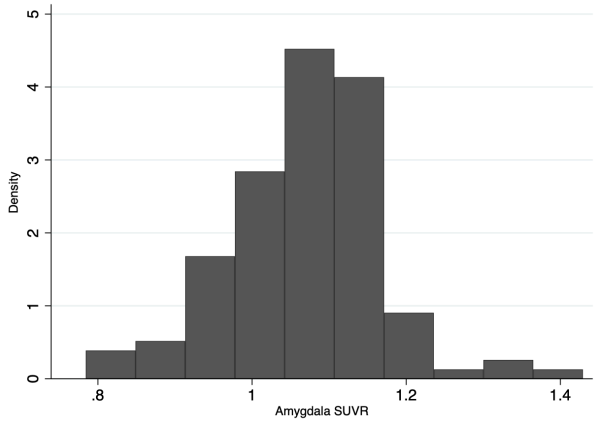


Figure 15. Histogram of across Cohort comparison of the amygdala SUVR between the CDUA group in Cohort One vs the CDUA group in Cohort Two

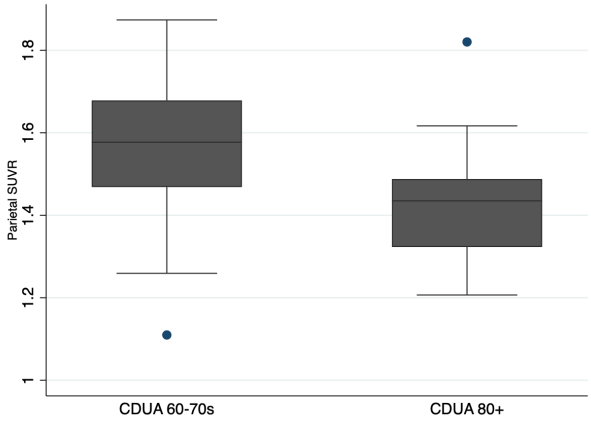


Figure 16. Box plot of across cohort comparison of the parietal SUVR between the CDUA group in Cohort One vs the CDUA group in Cohort Two

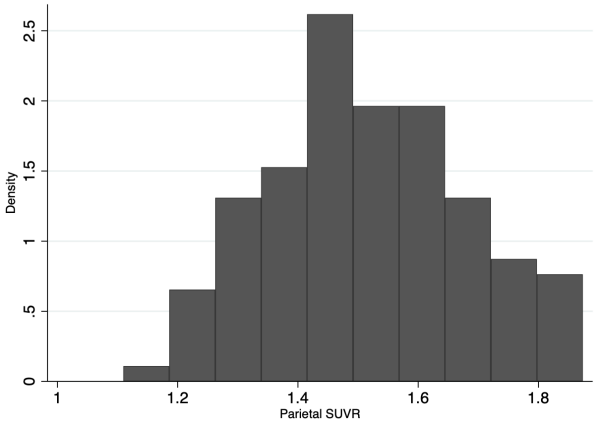


Figure 17. Histogram of across cohort comparison of the parietal SUVR between the CDUA group in Cohort One vs CDUA group in Cohort Two

5.4.5 AD Group

Table 13. Linear Regression Results for the comparison between AD groups vs Normal in Cohort One and Two, and the results for AD in Cohort One vs AD in Cohort Two.

** 95% CI = 95% confidence interval * adjusted for: age, gender, dos*

Linear Regression			
Variable,	**Mean (95%CI)**	**Coefficient (95% CI)**	**p-value**
Cohort One Normal vs AD			
Unadjusted Analysis			
Amygdala SUVR (Normal vs. AD), 1.068 (95%CI 1.047 to 1.088) vs. 1.038 (95%CI 0.938 to 1.139)		0.029 (95%CI -0.051 to 0.110)	0.473
Adjusted Analysis			
Amygdala SUVR		-0.056 (95%CI -0.181 to 0.069)	0.379
Unadjusted Analysis			
Parietal lobe SUVR (Normal vs. AD), 1.498(95%CI 1.466 to 1.530) vs. 1.267 (95%CI 1.220 to 1.314)		0.231 (95%CI 0.176 to 0.285)	<0.001
Adjusted Analysis			
Parietal lobe SUVR		0.278 (95%CI 0.192 to 0.363)	<0.001
Cohort Two Normal vs AD			
Unadjusted Analysis			
Amygdala SUVR (Normal vs. AD), 1.116 (95%CI 1.095 to 1.137) vs. 1.013 (95%CI 0.983 to 1.042)		0.103 (95%CI 0.066 to 0.140)	<0.001
Adjusted Analysis			
Amygdala SUVR		0.114 (95% CI 0.066 to 1.161)	<0.001
Unadjusted Analysis			
Parietal lobe SUVR (Normal vs. AD), 1.633 (95%CI 1.592 to 1.673) vs. 1.256 (95%CI 1.217 to 1.294)		0.377 (95%CI 0.321 to 0.433)	< 0.001
Adjusted Analysis			
Parietal lobe SUVR		0.352 (95%CI 0.281 to 0.423)	<0.001
Cohort One AD vs Cohort Two AD			
Unadjusted Analysis			
Amygdala SUVR (AD 80+ vs. AD 60-70), 1.038 (95%CI 0.938 to 1.139) vs. 1.013 (95%CI 0.983 to 1.043)		0.025 (95%CI -0.059 to 0.109)	0.055
Adjusted Analysis			
Amygdala SUVR		0.047 (95% CI -0.204 to 0.298)	0.712
Unadjusted Analysis			
Parietal lobe SUVR (AD 80+ vs. AD 60-70), 1.267 (95%CI 1.220 to 1.314) vs. 1.256 (95%CI 1.216 to 1.295)		0.011 (95%CI -0.05 to 0.729)	0.718
Adjusted Analysis			
Parietal lobe SUVR		0.010 (95%CI-0.176 to 0.197)	0.914

5.4.6 *The comparison between cohort one AD Group vs normal group*

For subjects in Cohort One, the mean amygdala SUVR was larger in the Normal group 1.068 (95%CI 1.047 to 1.088) compared to the AD group 1.038 (95%CI 0.938 to 1.139). There was no evidence of a difference in amygdala SUVR between these groups before 0.029 (95%CI -0.051 to 0.110, p=0.473) or after adjusting for confounding 0.056 (95%CI -0.181 to 0.069, p=0.379). In contrast, there was a difference in in parietal lobe SUVR between these groups before and after adjusting for confounding. The mean parietal lobe SUVR was 1.498 (95%CI 1.466 to 1.530) in the normal group compared to the AD group 1.267 (95%CI 1.220 to 1.314), difference before adjustment 0.231 (95%CI 0.176 to 0.285, p=<0.001) and difference after adjusting 0.278 (95% CI 0.192 to 0.363, p=<0.001). The following box plot show Cohort One's AD group amygdala and parietal lobe SUVR compared to the Normal group, and histograms for normal distribution.

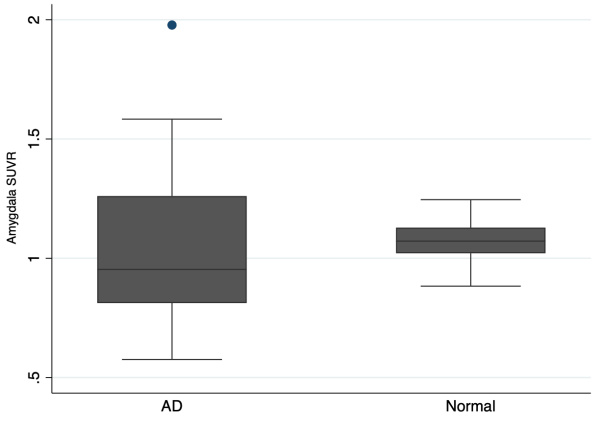


Figure 18. Box plot of Cohort One's AD group's amygdala SUVR compared to the Normal group

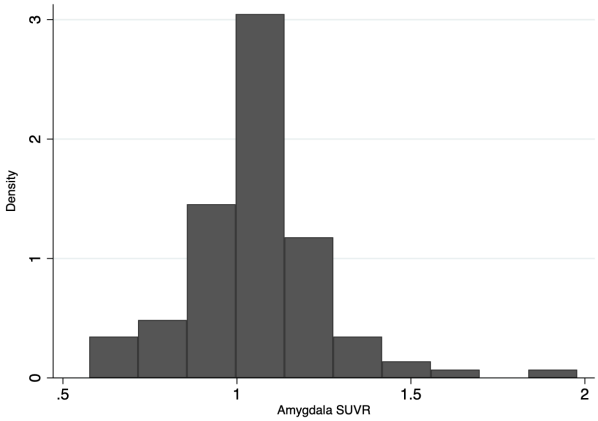


Figure 19. Histogram of Cohort One's AD group's amygdala SUVR compared to the Normal group

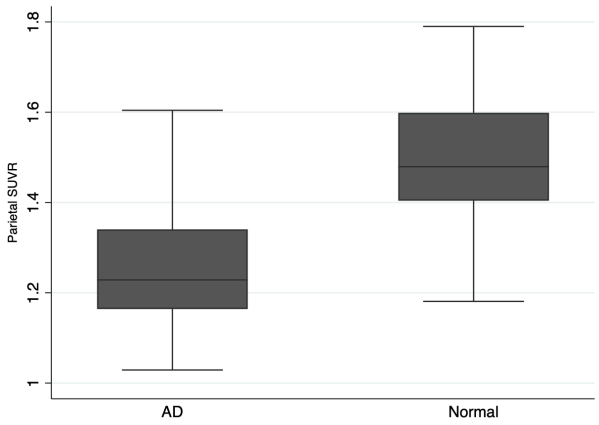


Figure 20. Box plot of Cohort One's AD group's parietal lobe SUVR compared to the Normal group

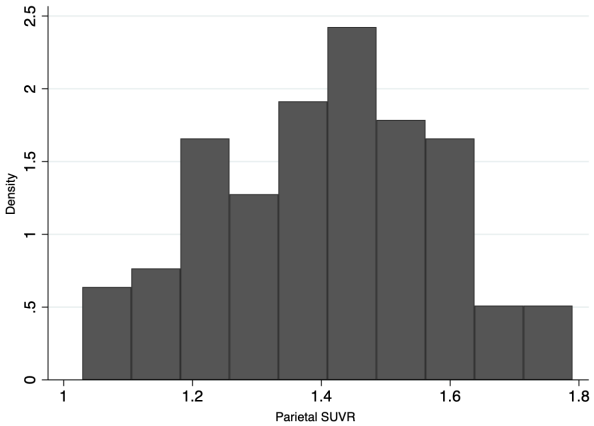


Figure 21. Histogram of Cohort One's AD group's parietal lobe SUVR compared to the Normal group

5.4.7 *The comparison between cohort two's AD group vs normal group*

For subjects in Cohort Two, the mean amygdala SUVR was larger in the Normal group 1.116 (95%CI 1.095 to 1.137) compared to the AD group 1.013 (95%CI 0.983 to 1.042). There was a difference in amygdala SUVR between these groups before 0.103 (95%CI 0.066 to 0.140, p =<0.001) and after adjusting for confounding 0.114 (95% CI 0.066 to 1.161, p =<0.001). Similarly, there was also a difference in parietal lobe SUVR between these groups before and after adjusting for confounding. The mean parietal lobe SUVR was 1.633 (95%CI 1.592 to 1.673) in the Normal group compared to the AD group 1.256 (95%CI 1.217 to 1.294), difference before adjustment 0.377 (95%CI 0.321 to 0.433, p =<0.001) and difference after adjusting 0.352 (95%CI 0.281 to 0.423, p =<0.001). The following box plot show Cohort Two's AD group amygdala and parietal lobe SUVR compared to the Normal group, and histograms for normal distribution.

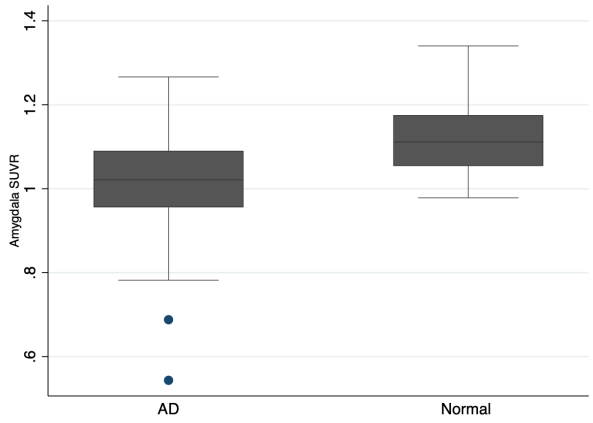


Figure 22. Box plot of Cohort Two's AD group's amygdala SUVR compared to the Normal group

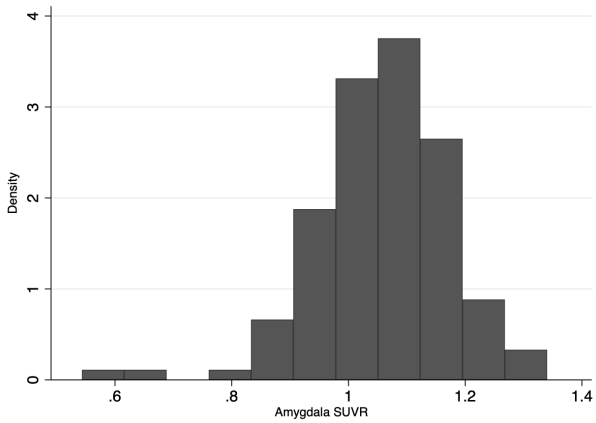


Figure 23. Histogram of Cohort Two's AD group's amygdala SUVR compared to the Normal group

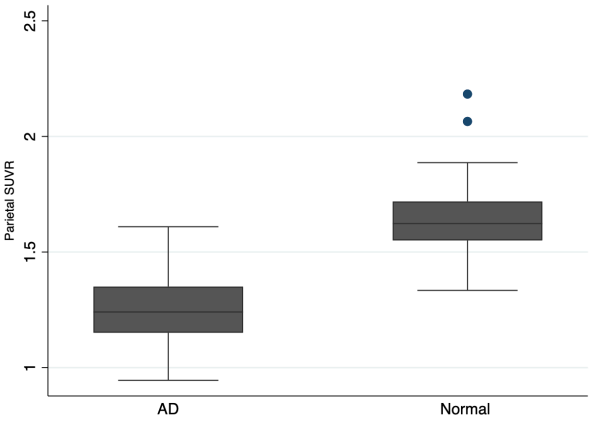


Figure 24. Box plot of Cohort Two's AD group's parietal lobe SUVR compared to the Normal group

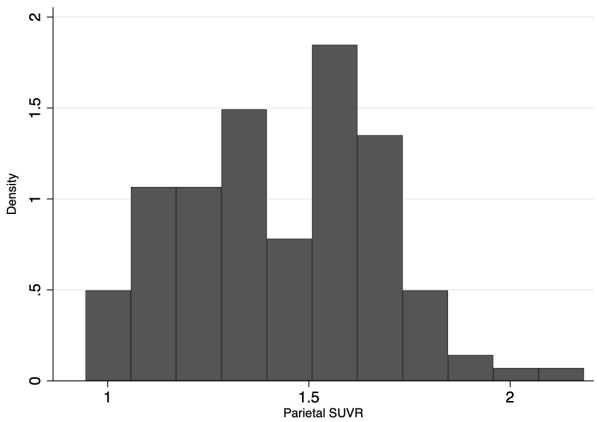


Figure 25. Histogram of Cohort Two's AD group's parietal lobe SUVR compared to the Normal group

5.4.8 *The comparison of cohort one's AD group vs. cohort two's AD group*

Between Cohorts One and Two's AD groups, the mean amygdala SUVR was larger in the Cohort One's AD group 1.038 (95%CI 0.938 to 1.139) compared to Cohort Two's AD group 1.013 (95%CI 0.983 to 1.043). There was no evidence of a difference in amygdala SUVR between these groups before 0.025 (95%CI -0.059 to 0.109, p=0.055) or after adjusting for confounding 0.047 (95% CI -0.204 to 0.298, p= 0.712).

Similarly, there was no evidence of a difference in parietal lobe SUVR between these groups before or after adjusting for confounding. The mean parietal SUVR was 1.267 (95%CI 1.220 to 1.314) in Cohort One's AD group compared to Cohort Two's AD group 1.256 (95%CI 1.216 to 1.295), difference before adjustment 0.011 (95%CI -0.05 to 0.729, p=0.718) and difference after adjusting 0.010 (95%CI-0.176 to 0.197, p=0.914). The following box plot show Cohort One's AD group amygdala and parietal lobe SUVRs compared to Cohort Two's and histograms for normal distribution.

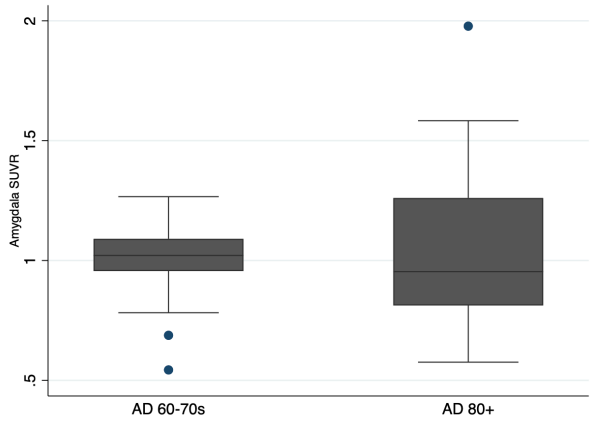


Figure 26. Box plot of across cohort comparison of the amygdala SUVR between AD group in Cohort One vs the AD group in Cohort Two

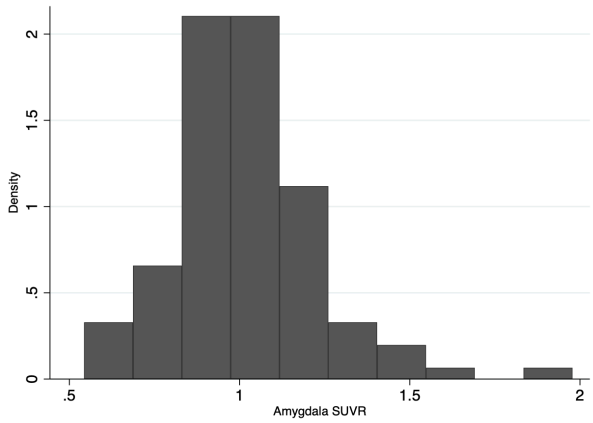


Figure 27. Histogram of across cohort comparison of the amygdala SUVR between AD Cohort One vs AD group in Cohort Two

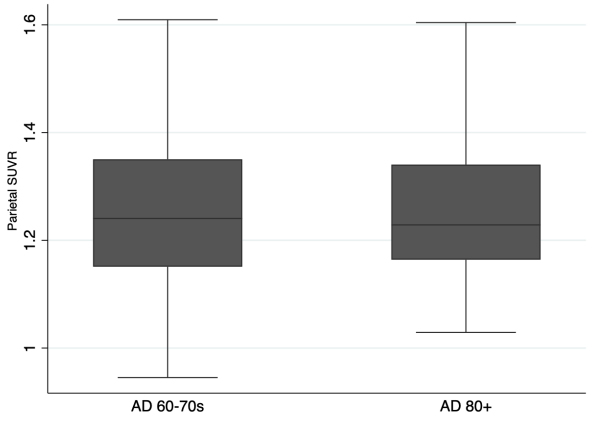


Figure 29. Box plot of across cohort comparison of the parietal SUVR between AD group in Cohort One vs the AD group in Cohort Two

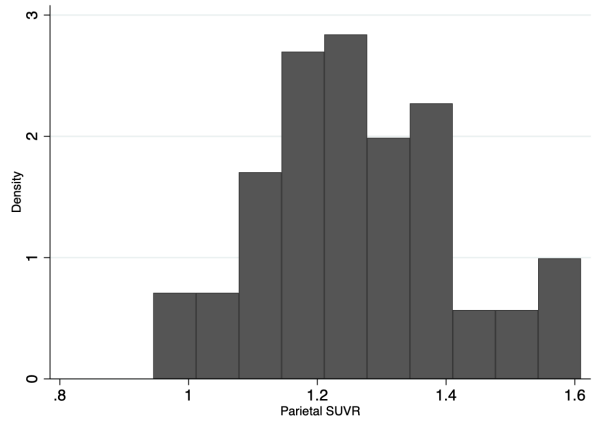


Figure 30. Histogram of across cohort comparison of the parietal SUVR between AD group in Cohort One vs the AD group in Cohort Two

5.5.9 Normal group

Table 14. Linear Regression comparison of Cohort One's Normal group vs. Cohort Two's Normal group ** 95% CI = 95% confidence interval * adjusted for: age, gender, dos*

Linear Regression			
Variable,	**Mean (95%CI)**	**Coefficient (95% CI)**	**p-value**
Cohort One Normal vs Cohort Two Normal			
Unadjusted Analysis			
Amygdala SUVR (Normal 80s vs. Normal 60-70), 1.068 (95%CI 1.047 to 1.088) vs. 1.116 (95%CI 1.091 to 1.137)		-0.048 (95%CI -0.077 to -0.019)	0.001
Adjusted Analysis			
Amygdala SUVR		<0.001 (95%CI -0.112 to 0.111)	0.995
Unadjusted Analysis			
Parietal lobe SUVR (Normal 80+ vs. Normal 60-70s), 1.498(95%CI 1.466 to 1.530) vs. 1.633 (95%CI 1.592 to 1.673)		-0.135 (95%CI -0.185 to -0.084)	<0.001
Adjusted Analysis			
Parietal lobe SUVR		-0.196(95%CI -0.389 to -0.003)	0.046

5.5.10 *The comparison of cohort one's normal group vs. cohort two's normal group*

Between Cohorts One and Two's Normal groups, the mean amygdala SUVR was smaller in the Cohort One's Normal group 1.068 (95%CI 1.047 to 1.088) compared to Cohort Two's Normal group 1.116 (95%CI 1.091 to 1.137).There was evidence of a difference in amygdala SUVR between these groups before 0.048 (95%CI -0.077 to -0.019, p=<0.001) but not after adjusting for confounding <0.001 (95%CI -0.112 to 0.111, p=0.996).

In contrast there was a difference in parietal lobe SUVR between these groups before and after adjusting for confounding. The mean parietal lobe SUVR was 1.498(95%CI 1.466 to 1.530) in Cohort One's Normal group compared to Cohort Two's Normal group 1.633 (95%CI 1.592 to 1.673), difference before adjustment 0.135 (95%CI -0.185 to -0.084, p=<0.001) and difference after adjusting 0.196 (95%CI -0.389 to -0.003, p=<0.050). The following box plots show Cohort One's Normal group amygdala and parietal lobe SUVRs compared to Cohort Two's and histograms for normal distribution.

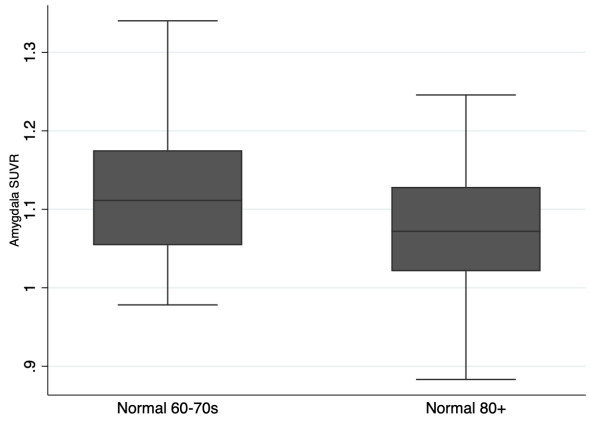


Figure 31. Box plot of across cohort comparison of the amygdala SUVR between the Normal group in Cohort One vs Normal group in Cohort Two

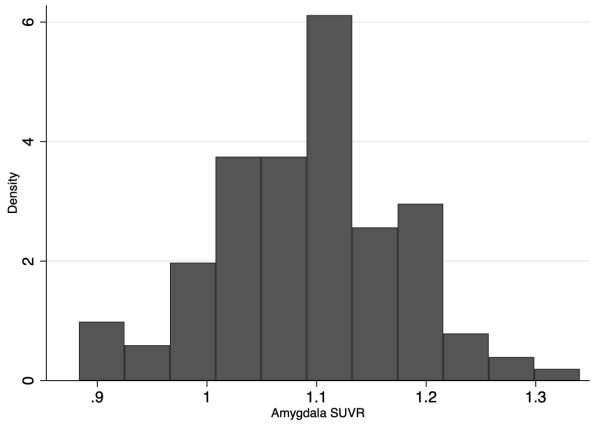


Figure 32. Histogram of across cohort comparison of the amygdala SUVR between the Normal group in Cohort One vs Normal group in Cohort Two

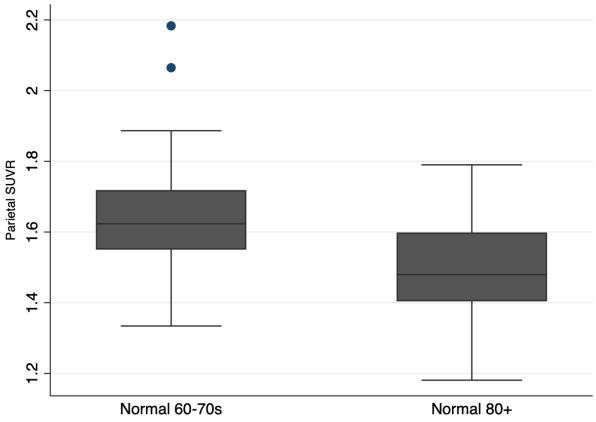


Figure 33. Box plot of across cohort comparison of the parietal lobe SUVR between the Normal group in Cohort One vs Normal group in Cohort Two

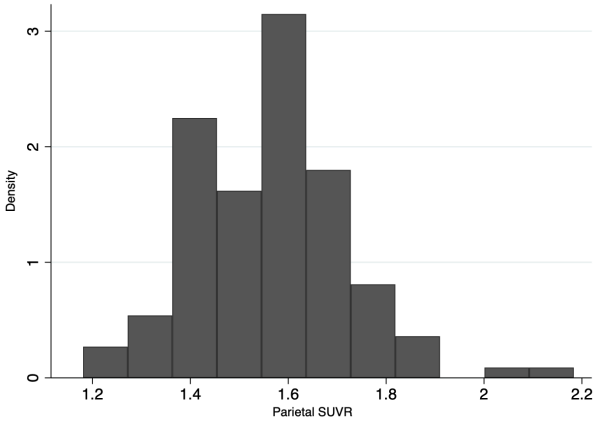


Figure 34. Histogram of across cohort comparison of the parietal lobe SUVR between the Normal group in Cohort One vs Normal group in Cohort Two

6 Discussion

6.1 Summary and interpretation of key findings

6.1.2 Primary outcome key findings

In Cohort One, abnormal amygdala metabolic reduction was seen in 4 subjects (8.9%) in the CDUA group, 2 subjects (5%) in the AD group with an overall rate of 6 subjects (7%) without parietal reduction suggesting pure LATE. Abnormal amygdala metabolic reduction was seen in 1 subject (2.2%) in the CDUA group, 5 subjects (12.8%) in the AD group with an overall rate of 6 subjects (7%) with parietal reduction, suggesting comorbid LATE/AD. This gives an overall rate of 12 subjects with suspected LATE presence in the CDUA and AD groups, combined being 14.3% (12/84), and 18% (7/39) in the AD group alone, and 11% (5/45) in the CDUA group alone.

In Cohort Two, abnormal amygdala metabolic reduction was seen in 2 subjects (2.7%) in the CDUA group, 7 (10.5%) subjects in the AD group, with an overall rate of 9 subjects (6.3%) without parietal reduction suggesting pure LATE. Abnormal amygdala metabolic reduction was seen in 9 subjects (13.4%) in the AD group, and none was seen in the CDUA group, with an overall rate of 9 subjects (6.3%) with parietal reduction, suggesting comorbid LATE/AD. This gives an overall rate of 18 subjects with suspected LATE presence in the CDUA and AD groups combined being 12.6% (18/142), and 23.9% (16/67) in the AD group alone, and 2.6% (2/75) in the CDUA group alone.

Results suggest that both pure LATE and comorbid LATE/AD is more common in the elderly cohort, being present in 7% of subjects compared to 6.3% of subjects in the younger cohort. Overall prevalence of amygdala reduction in AD subjects of approximately 18% and 23.5 % in Cohort one Two respectively is similar to that suggested in the literature (approximately 20% LATE) and supports using measured amygdala activity as a technique to further categorize these patients.

Prevalence of combined amygdala and parietal reduction and overall prevalence of amygdala reduction is similar across Cohort One and Two which is an unexpected finding. The prevalence of hippocampal involvement and more generalized medial temporal reduction that is not LATE related may be greater in Cohort Two. As there is no pathologic data assessing this relationship it may be that there is unrecognized amygdala disease in this combined group leading to the known more aggressive cognitive decline that is seen.

6.1.3 Primary outcome secondary key findings

We demonstrate that FDG-PET imaging with quantitation of the amygdala and parietal lobe can be used to detect a difference in metabolic activity in 60-70 age range, and disease progression is more severe than we anticipated for this age range.

As expected, we found the most cases of suspected LATE, and suspected comorbid AD and LATE in subjects with diagnosed AD. Subjects in the AD groups of both cohort one and two showed greater amygdala and parietal lobe metabolic reduction compared to the Normal and CDUA groups. Subjects with suspected LATE or comorbid AD and LATE cases showed the most atrophy. This aligns with previous literature considering that the deposition of TDP-43 starts in the amygdala and spreads to the hippocampus.

We were able to identify subjects with below-normal amygdala activity and a normal parietal lobe metabolism, which we suspect to be attributed to LATE, subjects with a below-normal amygdala and parietal lobe metabolism, which we suspect to be attributed to comorbid AD/LATE, and subjects with only a below-normal parietal lobe metabolism, which we suspect to be attributed to AD.

We were able to identify 8 subjects with suspected LATE, 6 subjects with suspected comorbid AD/LATE, and 21 subjects with suspect AD in Cohort One (age 80 and over). We were able to identify 9 subjects with suspected LATE, 40 subject with suspected AD, and 9 subjects with suspected comorbid AD/LATE in Cohort Two (age 60 to 70).

We expected to find the most cases of comorbid AD/LATE in the AD group, and the most cases of LATE in the CDUA group. This was true for Cohort One's groups and Cohort Two's AD group. In Cohort Two's CDUA group we found more cases of AD then LATE. We did not expect to find 2 LATE subjects in Cohort One's normal group.

6.1.4 Secondary outcomes key findings

We found older subject (80y.o above) with AD, and CDUA on average have greater amygdala and parietal lobe metabolic reduction compared to normal subjects of the same age but do not have greater amygdala and parietal lobe metabolic reduction compared to younger subjects (60-70y.o) of the same condition. Conversely, normal older subjects did experience greater parietal lobe metabolic reduction compared to normal younger subjects.

We found that in Cohort One's CDUA group, there was a difference in parietal lobe SUVR 0.132 (95%CI 0.052 to 0.211, p= 0.001) but not amygdala SUVRs compared to the Normal group, and the average parietal lobe SUVR in the CDUA group 1.421(95%CI 1.383 to 1.460) was smaller than the Normal group's 1.498(95%CI 1.466 to 1.530), which fits with AD trends. Whereas with Cohort Two's CDUA group, there was a difference in amygdala SUVR 0.041 (95% CI 0.002 to 0.079, p=0.038) but not parietal lobe SUVR, compared to the Normal group, and the average amygdala SUVR was smaller in the CDUA group 1.092 (95%CI 1.071 to 1.113) than the Normal group's 1.116 (95%CI 1.095 to 1.137), which fits with LATE trends. Cohort One's and Cohort Two's CDUA result demonstrate amygdala or parietal regions metabolic activity are reduced compared to the Normal group. But there was no difference between the younger Cohort Two and the older Cohort One after adjusting for confounding, which suggest amygdala and parietal lobe metabolic rates are reduced compared to normal subjects but are not reduced further with age.

We found that in Cohort One's AD group, there was a difference in parietal lobe SUVR 0.278 (95%CI 0.192 to 0.363, p=<0.001) but not amygdala SUVR compared to the Normal group after adjusting for cofounding, and the average parietal lobe SUVR in the AD group 1.267 (95%CI 1.220 to 1.314) was smaller than the Normal group's 1.498(95%CI 1.466 to 1.530), which fits with AD trends. Whereas with Cohort Two's AD group, there was a difference in both amygdala SUVR 0.114 (95% CI 0.066 to 1.161, p=<0.001) and parietal lobe SUVR 0.352 (95%CI 0.281 to 0.423, p=<0.001) compared to the Normal group after adjusting for cofounding, and the average amygdala SUVR at 1.013 (95%CI 0.983 to 1.042), and parietal lobe SUVR at 1.256 (95%CI 1.217 to 1.294) were both smaller in the AD group than in the normal group 1.116 (95%CI 1.095 to 1.137), and 1.633 (95%CI 1.592 to 1.673) respectively, which fits with comorbid AD and LATE. Cohort One's and Cohort Two's AD result also demonstrate amygdala or parietal regions metabolic activity are reduced compared to the Normal group. There was no difference between the younger Cohort Two

and the older Cohort One after adjusting for confounding, which suggests amygdala and parietal lobe metabolic rates are reduced compared to normal subjects but are not reduced further with age.

However we found that in the comparisons of Cohort One's Normal group with Cohort Two's Normal group, there was a difference in parietal lobe but not amygdala SUVR after adjusting for confounding: the parietal lobe SUVR was smaller in the older cohort compared to the younger, which suggests in normal subjects biological ageing causes the parietal lobe SUVR to decrease, but not the amygdala SUVR.

6.2 Comparison with previous studies

Previous studies have assessed FDG-PET's utility in the identification of LATE. However, there have not been exploratory studies analysing SUVRs in different cohorts. Thus, direct comparison with previous studies is not possible. The findings of this study will add to current research conducted on FDG-PET for the identification of LATE in elderly subjects with AD and CDUA.

The findings indicate that descriptive SUVRs of amygdala and parietal lobe metabolic activity could be used to identify suspected LATE and differentiate between AD, CDUA, Normal, and comorbid AD and LATE.

The findings on its ability to identify LATE are inconclusive as we are only able to locate suspected LATE. However, without a post-mortem autopsy follow-up study there is no method of knowing the definitive status. A follow-up study would be required to evaluate the sensitivity and specificity of the diagnostic accuracy of using amygdala and parietal lobe SUVRs as a biomarker for LATE status.

6.3 Defining the role of SUVR in the clinical pathway

At present we are unable to define the role of amygdala and parietal lobe SUVRs in the clinical pathways, as we are unable to prove its diagnostic utility to identify LATE. However, there is little information on amygdala SUVRs, so this exploratory study provides descriptive information regarding the difference in amygdala and parietal lobe metabolic activity for AD, CDUA and Normal subjects in different elderly age groups, which may serve as groundwork for future studies. It is possible that with more detailed information, such as that provided in this review, researchers will have greater confidence to test if amygdala and parietal lobe SUVR could identify LATE. Future studies are required to assess the predictiveness of analysis on amygdala and parietal lobe SUVR for identifying LATE.

If future research proves analysis on amygdala and parietal lobe SUVRs helps to diagnose LATE it will provide a method of utilising FDG-PET imaging, which is widely available and safely used for patients with cognitive decline and dementia. Our findings are an important step in understanding the relationship between SUVRs in different cohorts which may pave the way for future research in predicting LATE status.

6.4 Defining the population that would benefit the most from this study

The population that would benefit the most from this study are elderly subjects with AD, due to the high prevalence of comorbid AD and LATE, and CDUA subjects, as LATE presents with particular clinical features such as memory impairments and overall cognitive decline. Being able to predict LATE status at earlier stages can provide valuable information on probable prognosis and course of the disease for the patients and their families.

6.5 Research significance

An exploratory analysis of elderly subjects may provide valuable information on the potential predictive abilities of FDG-PET using SUVRs to identify suspected LATE cases. Information from this study may point towards a direction for future research in the hopes of filling the void for an ante-mortem method of identifying suspected LATE, thus allowing diagnosis earlier in the clinical pathway.

6.6 Strengths and limitations

Strengths:

Our comparator (Normal group) was matched for age to our cohorts which, in return give us a baseline that accounts for normal biologically aged brains, to compare against CDUA and AD groups.

Possible sources of cofounding such as age, gender, and date of scan, were explored and accounted for in the adjusted regression models.

Limitation:

Although comparisons were defined a-priori, we have conducted multiple comparisons between different groups of patients. Therefore, it is possible that we could have falsely rejected the null hypothesis in some of the analysis, when the null hypothesis is actually true. There is a known issue with multiple comparisons which stems from the fact that if p=0.05 this there is a 5% risk of incorrectly rejecting the null hypothesis.

For identified suspected cases, a normal range is also known as a 'reference interval'. Being below the reference interval does not mean that they are abnormal, because even in an absolutely normal group we would still except to find 2.5% of subjects below the normal range (Whyte and Kelly, 2018). which we did find in Cohort One's Normal group, thus it is likely that we are overestimating suspected cases.

The number of subjects from the ADNI database was not a match between Cohorts One and Two as there was a need to increase the reliability of the Normal SUVR mean, so we included all subjects meeting the inclusion criteria. However, since we included all subject selections, bias was reduced. Unfortunately, sample size was small, which reduces the power of the study and increases the margin of error. It is more likely to accept a false negative (type II error) and inflates the effect size estimation. As a consequence, the study may not be able to detect a statistically significant result.

All analysis was descriptive, and there was little scope for investigation of sources of comorbidity. As a result, potential sources of bias could neither be confirmed nor excluded.

As there is no reference standard from the average LATE-NC parietal and amygdala lobe SUVR, our results can only point towards suspected TDP-43 subjects which are deemed suspected under our hypotheses. Results are non-definitive.

We also planned to analyse other pathways of dementia, such as frontotemporal lobar dementia, and Lewy body dementia, to see how the amygdala and parietal lobe were affected in these groups. However, owing to time constraints, this part of the analysis was left out.

As there were no confirmed diagnoses with a post-mortem biopsy for TDP-43, we were unable to compare our results to a definitive outcome. Therefore, this explorative study will require further research to include post-mortem results in the future.

7. Conclusion

In summary, this dissertation has demonstrated that FDG-PET can be used to measure and identify abnormal metabolic activity in the amygdala and parietal lobe regions, of both age ranges 60-70 and 80y.o and above, in subjects with AD, CDUA, and Normal.

Further more results support using measured amygdala activity as a technique to further categorise CDUA and AD patients to determine suspected LATE status. However, without a follow-up study, suspected LATE, AD and comorbid AD/LATE status cannot be confirmed. Since there currently is no way to definitively diagnose LATE and Comorbid AD/LATE status in the ante-mortem setting.

Categorisation of suspected LATE cases could be used for many purposes, including advising individuals about their future disease course, informing decisions about care and recommendations surrounding follow-up, selecting patients for involvement in intervention trials, and planning health care services that can support the future burden of LATE.

8. Reference

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9. Appendices

APPENDIX A. Study Protocol

Quantitative FDG-PET brain imaging for the differentiation of LATE neurodegeneration

Short title: FDG-PET for differentiation of TDP-43

Protocol version: 1

Protocol Number : RGS5282

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Project Summary

Cognitive impairment is common, particularly in the elderly and is mostly due to build-up of abnormal proteins in the brain that affects the neurons, leading to abnormal function and eventually death of nerve cells.

The most common cause is related to amyloid build up, which contributes to the development of Alzheimer's disease (AD,) people typically presenting initially with memory loss. Other proteins, including Tau and Alpha synuclein, tend to accumulate in different parts of the brain and lead to impaired neuronal function causing problems with other areas of brain function.

More recently, a protein TDP43 has been found to accumulate in the brains of elderly people who can develop symptoms of cognitive decline indistinguishable from AD. This is thought to contribute to the cognitive decline in up to 40% of elderly people over 80 years of age.

Diagnosing this condition is not possible with current available investigations. The only possible way is with a brain biopsy after subjects are deceased. More recent literature has suggested that metabolic brain imaging looking at neuron glucose metabolism with particular attention to a part of the brain called the amygdala may be able to determine which patients are likely to have this protein accumulation.

We plan to analyse amygdala activity in patients that have had previous brain scans using FDG PET (Fluorodeoxy glucose, Positron Emission Tomography) referred with cognitive decline. Amygdala metabolic reduction in these patients will be compared to amygdala activity in the scans of elderly patients used as patient controls for other studies, which are available from online clinical databases.

The rates of amygdala metabolism reduction will be correlated to the presence of other causes of cognitive dysfunction as determined by their FDG brain scan imaging. We expect up to 40% of people referred for imaging for possible AD will have a reduced amygdala metabolism, some of whom will have further scan abnormality that suggest AD or an alternative cause of cognitive impairment. This has not been previously assessed based on a typical cohort of patients referred for assessment having various potential causes of cognitive impairment. It will also allow us to assess the rate of amygdala metabolism reduction in patients referred with cognitive impairment who have no likely cause based on their FDG imaging and these may represent a group of patients with TDP43 accumulation as an isolated, previously unrecognised cause for neurologic decline.

As this condition tends to occur in patients over 80 years of age, we plan to do a further database search of patients 60 -70 years old to note differences rates of amygdala reduction in this age group.

Rationale / Background

Neurodegenerative disease is a common cause of cognitive decline, having an increasing prevalence with ageing (Hugo and Ganguli, 2014). Cognitive decline related to TDP 43 (Transactive response DNA binding protein of 43 kDa TDP-43) proteinopathy in limbic brain structures is more commonly seen in elderly patients (past 80 year of age) and can lead to an amnestic clinical presentation that may be indistinguishable from AD (Zhang et al., 2020).

LATE neuropathologic changes (LATE-NC) are present in > 20% of individuals over 80 years of age (Nelson et al., 2019). While often associated with Alzheimer's disease neuropathologic changes (AD-NC) including hippocampal sclerosis (Davidson et al., 2011), AD-NC may be mild in patients of advanced age with progressive cognitive decline and it is suggested the presence of TDP 43 proteinopathy is a causal or comorbid pathology that increases the likelihood of progression to cognitive decline (Thomas et al., 2020).
A staging system based on neuropathologic assessment suggests TDP43 deposition in the amygdala as an initial site (Stage 1) with subsequent involvement of the hippocampus (Stage 2) and middle frontal gyrus (Stage 3) (Josephs et al., 2013). AD-NC is also progressive with mesial temporal, and later temporoparietal involvement (Whitwell et al., 2011).

Positron emission tomography (PET) using Fluorodeoxyglucose (FDG) is an imaging technique that allows assessment of brain neuronal activity and is routinely used in the assessment of cognitive decline through neurodegeneration in aetiology, the distribution of the cortical hypometabolism suggesting the potential underlying neurodegenerative process. In AD this typically involves temporoparietal lobes, precuneus and posterior cingulate (Marcus, Mena and Subramaniam, 2014). FDG PET has been shown to be more accurate than clinical criteria when compared to the final neuropathologic diagnosis of dementia subtype (Berti, Pupi and Mosconi, 2011).

Brain FDG image analysis is typically with visual inspection of relative cortical activity, often in conjunction with software analysis of imaging data compared to a normal database (Patterson, Lilien, Takalkar and Pinkston, 2011). In some cases, patients with cognitive decline, and possible MCI/AD may have non-specific imaging changes or may have no metabolic changes in a

distribution to suggest AD or alternative neurodegenerative dementia, such as Lewy Bodies (DLB) or a frontotemporal dementia (FTD) (Tartaglia, Rosen and Miller, 2011). This may relate to MCI in the setting of mild cognitive decline or an unrecognized alternative non-neurodegenerative cause of dementia, such as a vascular aetiology (particularly small vessel), toxic or infective aetiology. In the elderly patient group TDP-43/LATE as a cause for amnestic cognitive decline may be an unrecognized cause in a portion of these patients as they may have less severe AD-NC and are less likely to have characteristic lobar changes, particularly parietal lobe reduction.

A recent study suggested that FDG activity in mesial temporal structures could differentiate TDP-43-positive patients from TDP-43-negative patients with AD-NC spectrum changes (Buciuc et al., 2020), and FDG activity in mesial temporal structures, the amygdala in particular.

Objectives

Objective: To assess the prevalence and degree of amygdala hypometabolism in elderly patients referred to a tertiary hospital for assessment of cognitive decline.
Hypothesis: Patients over 80 years of age with cognitive decline having FDG PET brain scan assessment for neurodegenerative disease should have a higher prevalence of amygdala metabolic reduction than patients between 60 - 70 years of age.

Project Design

Project Design
Cross-sectional observational study of semi-quantitatively assessed amygdala activity.
Source and Selection of Participants
Patients from Fiona Stanley Hospital and Sir Charles Gairdner Hospital who have had FDG PET brain scans from 2010 – 2020; search terms Alzheimer or cognitive or dementia.

1. Expected number of patients > 80 years of age approximately 250 patients.
2. Expected number of patients 60 – 70 years of age 250 patients.
3. Online ADNI “normal” > 80 years of age, approximately 60 patient scans. To define a normal range for amygdala activity using our amygdala mask.

Participant inclusion criteria:

1. Online patient data – Patients being normal based on clinical and neurocognitive assessment as defined by the contributing research group. Meeting age criteria at the time of imaging.
2. Images in the WA Health PACs system – Based on search terms and meeting age criteria at the time of imaging.

Participant exclusion criteria:

Images of WA Health patients on PACs only - Unsuccessful/non diagnostic scans, Parkinson's diagnosis, substance abuse (drug/alcohol), abnormal growths (cancer, leukaemia, lymphoma, lesions, malignancy [non-metastatic and metastatic]), vascular-related disease (vascular dementia, prior stroke, multi-infarct, infarct, hypertension, major mental illnesses (diagnosed bipolar, schizophrenia, or depression), head injury or trauma and structural brain disease (infection, NPH, infection, previous HSV).

The only patient data accessed with be that available on the WA Health PACs system, from the clinical request and the imaging scan report.

Participant withdrawal criteria :

Not applicable

Bias:

Measures taken to minimise/avoid bias, including randomisation and blinding.

Non-randomised. No bias as software assessment of amygdale activity.

Blinding and Randomisation:

Maintenance of any blinding records or randomisation codes and procedures for breaking codes.

NA

Data analysis:

Included patients' data will be categorised into diagnostic groups based on the likely cause for cognitive decline as determined by the result of their FDG brain PET. This will be based on a diagnostic statement on the clinical report or if equivocal, the scan data will be reviewed by two Nuclear Medicine PET neuroimaging specialists with a consensus diagnosis made.

The groups will include:

1. Normals – Normal appearing FDG PET, no cause for cognitive decline demonstrated

2. AD – Features including parietal lobe hypometabolism, suggesting or consistent with AD (Alzheimer's disease)
3. FTD – Features including frontal or temporal lobe hypometabolism suggesting or consistent with FTD (frontotemporal dementia).
4. LBD – Occipital lobe hypometabolism suggesting or consistent with LBD (Lewy Body dementia)

Subject emission PET data from the above four groups will have amygdala metabolic activity assessed. This will be done by co-registering their FDG PET volumetric data to a 3-D brain atlas, median activity in the amygdala extracted based on volumetric coordinates.

A ratio of median count in the amygdala and median counts from the pons will be performed with an amygdala-to-pontine ratio (A/P Ratio) obtained. The pons chosen as this organ is not typically involved in the most common neurodegenerative dementias, is anatomically well defined and accurately co-registered and was the reference area in the Buciuc et al. paper.

The A/P Ratio for each patient diagnostic group will be compared to the reference range and normal cut off (-2SD) as determined by analysis of the age-matched normal data sourced from the online database.

Prevalence of abnormal amygdala activity will be compared between the diagnostic groups in the > 80y.o as well as the 60 -70y.o patient data.

Treatment of Participants

Description and justification for treatments, interventions or methods to be utilised.
Cross-sectional study with no follow up. Data extracted from WA Health PACS imported onto analysis software.

Assessment of Efficacy

Outcomes:

NA

Efficacy assessment:

NA

Assessment of Safety

Risks and Benefits

We believe that there is no foreseeable harm, risk, discomfort or inconvenience to study participants as no patient contact is required, and the design of the study is such that no investigations or interventions will be performed. The participants will not be subjected to any procedures, treatments or questionnaires. All medical data being requested has already been collected in the standard course of the participants' referral, performance of the scan and its interpretation.

The potential benefit to come from the research outcome, is to determine if semi quantitative measurement of amygdala metabolic activity may identify a subgroup of cognitively impaired patients who may have isolated or coexisting TDP43 encephalopathy as an unsuspected cause. This will have prognostic and potentially therapeutic implications.

Safety

As no patient contact is required and no investigations or interventions will be performed, we do not foresee any patient safety issues.

Data Management, Statistical Analysis and Record Keeping

Statistics and Interim Analysis:

Single time point, cross sectional

Sample Size:

Sample determined by data base search result.

Study Power and Significance:

Descriptive study no power calculation possible.Based on the analysis from the online normal data an amygdala/pontine ratio of - 2 SD will be used as lower cut-off for normal.

Statistical plan deviations:

Descriptive observational study

Selection of participants for analyses:

All eligible participants.

Data Management:

Downloaded FDG Brain PET data will be analysed on a Medical Physics computer at FSH. The subject data will remain on the PACs system and the copied trial analysed data will remain at FSH. The de-identified data will be stored on secure servers at Fiona Stanley Hospital for at least 7 years post project completion and will be accessible only to the research team.

Procedure for accounting for missing, unused, and spurious (*false*) data:

NA

Monitoring/Audit

Monitoring, Audit and Regulatory Inspections Statement:

No external sponsor. Monitoring and audit by HREC and SMAHS governance bodies permitted and welcomed.

Procedures for Monitoring and auditing:

The sponsor may nominate the form of monitoring and auditing and will indicate the times of audit visits.

Quality Control And Quality Assurance

Compliance statement

The project and data generated will be conducted with the principals of Good Clinical Practice observed.

Quality control

Data analysis will be done using appropriate software.

Ethics

Minimal ethical considerations. De-identified group analysed data. General consent given at the time of imaging. See attached consent waiver justification.

Budget, Financing, Indemnity And Insurance

Budget, financing, indemnity and insurance, if not addressed in a separate agreement.
In kind support from hospital. No direct costs.

Publication

Investigators aim to publish the outcomes of this study in a peer-reviewed medical journal.

References

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8. Utility of FDG-PET in diagnosis of Alzheimer-related TDP-43 proteinopathy. Neurology 2020. 95(1), pp.e23-e34.

APPENDIX A: Ethics

Ethics Approved - HREC

PRN:	RGS0000005282
Project Title:	**Semiquantative assessment of amygdala activity using FDG PET in the differentiation of TDP43 encephalopathy.**
Protocol Number:	Version 1

Thank you for submitting the above research project for ethical review. This project was considered by the South Metropolitan Health Service Human Research Ethics Committee at its meeting held on 27th September 2022.

I am pleased to advise you that the above research project meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007)* and ethical approval for this research project has been granted by South Metropolitan Health Service Human Research Ethics Committee.

The nominated participating site(s) in this project is/are:
Fiona Stanley Hospital and Sir Charles Gairdner Hospital
[Note: If additional sites are recruited prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the Human Research Ethics Committee (HREC). Notification of withdrawn sites should also be provided to the HREC in a timely fashion.]
The approved documents include:

Document	Version	Version Date
5282_WA Health Ethics Application Form (WAHEAF)	1	10/08/2022

Ethical approval of this project from South Metropolitan Health Service Human Research Ethics Committee is valid from 27 September 2022 to 27 September 2027 subject to compliance with the 'Conditions of Ethics Approval for a Research Project' (Appendix A).
A copy of this ethical approval letter must be submitted by all site Principal Investigators to the Research Governance Office or equivalent body or individual at each participating institution in a

timely manner to enable the institution to authorise the commencement of the project at its site/s. Should you have any queries about the South Metropolitan Health Service Human Research Ethics Committee's consideration of your project, please contact the Ethics Office at SMH.WAHREC@health.wa.gov.au or on 08 9141 2064. The HREC's Terms of Reference, Standard Operating Procedures and membership are available from the Ethics Office or from https://ww2.health.wa.gov.au/About-us/South-Metropolitan-Health-Service/Involving-our-community/Research-at-South-Metropolitan-Health-Service/For-South-Metropolitan-Health-Service-researchers.

The HREC wishes you every success in your research.

Yours sincerely

Dr Natalie Giles

Delegate of the Chair

South Metropolitan Health Service Human Research Ethics Committee

APPENDIX B: ADNI

Open source - Account has been established *https://adni.loni.usc.edu*