A Study of Interactions Between Memory Disorders and Epilepsy: Epileptic Seizures in Dementia, Contrasted with Transient Epileptic Amnesia

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

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“My advice is, never do tomorrow what you can do today. Procrastination is the thief of time. Collar him!”

“It's in vain to recall the past, unless it works some influence upon the present.”

“[W]e talk about the tyranny of words, but we like to tyrannise over them too; we are fond of having a large superfluous establishment of words to wait upon us on great occasions; we think it looks important, and sounds well. As we are not particular about the meaning of our liveries on state occasions, if they be but fine and numerous enough, so, the meaning or necessity of our words is a secondary consideration, if there be but a great parade of them. And as individuals get into trouble by making too great a show of liveries, or as slaves when they are too numerous rise against their masters, so I think I could mention a nation that has got into many great difficulties, and will get into many greater, from maintaining too large a retinue of words.”

Charles Dickens (1850) *David Copperfield*

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ABSTRACT

The term dementia refers to a group of progressive neurodegenerative diseases in which patients experience a range of cognitive symptoms, with memory impairment the most common. These patients are also at risk of experiencing epileptic seizures. Transient Epileptic Amnesia (TEA) is a syndrome of temporal lobe epilepsy in which the principal manifestation of a seizure is a brief episode of amnesia during which other mental functions are predominantly or entirely preserved. Patients with TEA describe persistent memory impairments which are distinct from their seizures. In this thesis two studies are described which look in detail at each of these conditions separately. The demographic features, seizure presentations and cognitive profiles of these two groups are then compared in order to improve our understanding of these under-recognised conditions, and to assist clinicians tasked with their diagnosis.

It has been known for over a century that patients with Alzheimer's disease (AD) can experience epileptic seizures. However, the degree to which the risk of epilepsy is increased in these patients remains unclear. Seizures were long thought of as a feature of advanced disease in these patients, only occurring several years after the onset of symptoms. However, more recent evidence has suggested that seizures can occur at an early stage of the disease, maybe even prior to the onset of memory symptoms. This suggests that seizures in this population may be a cause of decline, rather than purely a marker of severe disease. The aim of the work reported in this thesis is to investigate a cohort of patients with dementia and Mild Cognitive Impairment (MCI), recruited from a regional memory clinic in order to determine the prevalence, clinical features and prognosis of epileptic seizures in patients with MCI and all forms of dementia. A UK-based, prospective study of this nature has not been conducted before

144 patients with MCI and dementia were recruited from the Exeter memory clinic. Diagnoses were confirmed using established diagnostic criteria, together with a group of 80 age- and gender- matched healthy control subjects. Participants underwent a clinical interview and cognitive testing, in the company of a reliable informant, who also completed further questionnaires. Cognitive testing and informant questionnaires were repeated following a 12-month interval.

A prevalence of epilepsy of between 12.5 and 25.7% is identified in this population. Patients in whom a clinical suspicion of epilepsy was suspected were no different to those in whom there was no clinical evidence of epilepsy in terms of age of onset or cognitive performance at their initial study assessment. However epilepsy patients scored higher on the informant questionnaires, suggesting a greater impairment and increased care requirements. At the time of their 12-month assessment, the patients in whom epilepsy had been identified performed significantly worse on cognitive testing, suggesting that the presence of seizures was associated with a more rapid decline in this group.

The concept of TEA has been established for over 25 years. These patients describe amnesic episodes which are brief and frequently occur upon waking. Seizures may be associated with olfactory hallucinations. Studies have shown that they respond well to anti-epileptic medications. An initial cohort of 50 patients with TEA was described in 2007. In this thesis a further cohort of 65 patients is described and combined with the original 50 patients in order to clarify and more fully describe the demographic, clinical and neuropsychological features of this condition. Through this largest ever cohort of TEA patients it is shown that the mean age of onset of TEA is 61.7 years, and that men are more commonly diagnosed than women. Seizures in TEA typically last from 15 to 30 minutes and frequently occur on a monthly basis. 93% of patients in this study reported cessation of seizures following the initiation of medication. Despite this, interictal memory concerns are common: including autobiographical amnesia, accelerated long-term forgetting and topographical amnesia.

In comparing these two groups it is shown that patients who experience TEA are younger than those who experience epileptic seizures as a feature of MCI or dementia. They perform better on cognitive testing and neuroradiological investigations are more likely to be normal. In TEA, ictal amnesia is more likely to be the sole feature of a seizure, and olfactory hallucinations are more common. Patients with dementia are more likely to experience periods of unresponsiveness. Patients who develop epileptic seizures as a feature of MCI or dementia demonstrate significant cognitive decline over time, whereas cognitive performance is typically stable in patients with TEA.

CHAPTER ONE: GENERAL INTRODUCTION

1.1 INTRODUCTION

The work reported in this thesis investigates the prevalence and clinical features of epileptic seizures in dementia. Whilst the association between dementia and epilepsy has been well known for over a century, it remains incompletely understood, disputed and under-recognised. Previous studies have reported markedly discrepant rates of epilepsy in patients with dementia as well as inconsistent clinical features and long-term effects (Noebels, 2011, Vossel et al., 2013, Horvath et al., 2016).

One of the reasons why these questions remain unresolved is the blurred line between epilepsy in dementia and memory loss in epilepsy. Patients with epilepsy frequently report problems with memory that can sometimes resemble dementia (Giovagnoli et al., 2014, Leeman-Markowski and Schachter, 2016, Rayner and Tailby, 2017). This is especially true of epilepsy involving the temporal lobes (Tramoni Negre et al., 2017). Transient Epileptic Amnesia (TEA) - a form of epilepsy in which the principal manifestation of a seizure is transient, isolated impairment of memory is a specific example of this phenomenon and seizures in this condition have been shown to frequently originate from the temporal lobes (Butler et al., 2013, Butler et al., 2007). Many patients with this condition are initially suspected of having dementia before a final diagnosis is made, often many years after seizures initially start (Zeman et al., 1998, Butler et al., 2007, Mosbah et al., 2014). It is clear that improvements in our understanding of both epilepsy in dementia and of TEA are required in order to expedite the diagnostic process and facilitate prompt treatment of these two conditions, related in their predilection for involvement of the temporal lobes.

There are three principal questions under investigation in this thesis: what is the prevalence of epileptic seizures in patients with dementia? Is there a relationship between a clinical suspicion of epilepsy and the rate of cognitive decline in these patients? How do patients who develop epilepsy as a feature of their dementia compare with patients who experience memory impairment as a feature of their epilepsy - and in particular those patients with Transient Epileptic Amnesia?

In this introductory chapter I review the history of the association between dementia and epilepsy and summarise the clinical, and pathophysiological features of the most common dementia subtypes. In section 1.5 I introduce the concept of TEA and outline many of the features of this epilepsy syndrome, before, in section 1.6, comparing epilepsy in dementia and TEA and the clinical questions posed by a patient with a presentation of transient amnesia.

1.2 THE HISTORICAL BACKGROUND OF EPILEPSY IN ALZHEIMER'S DISEASE

1.2.1 ALZHEIMER'S 1911 CASE REPORT

In 1907 Alois Alzheimer reported the case of Auguste D; in it he describes many of the key features that would come to define the condition which would later bear his name (Alzheimer, 1907, Stelzmann et al., 1995).

> Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When reading a test, she skips from line to line or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing, she repeats separate syllables many times, omits others, and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions ("milk-pourer'' instead of cup); sometimes it is obvious that she cannot go on. Plainly, she does not understand certain questions.

Whilst the details of this case have been repeated and discussed on many occasions over the following century, for the purposes of this thesis it is a later case, again reported by Alzheimer, which holds more interest. This case, reported 4 years later, is that of Johann F (Alzheimer, 1911, Moller and Graeber, 1998).

> Quiet; since 1/2 year very forgetful, clumsy, could not find his way, was unable to perform simple tasks or carried these out with difficulty, stood around helplessly, did not provide himself with lunch, was content with everything, was not capable of buying anything by himself and did not wash himself. Very dull, slightly euphoric, slow in comprehension, unclear. Slowed speech, rare answers, frequent repetition of the question.

Whilst this patient again describes many of the features of Alzheimer's disease, it is what happens two years after that initial presentation which is of particular interest (Moller and Graeber, 1998).

> 3 Feb. 1909. Epileptiform seizure lasting a few minutes. Twitching of his face.
> 6 Feb. 1909. Right-sided facial palsy.
> 9 Feb. 1909. No obvious facial weakness anymore. Repeat tests of blood and serum yield the same negative results as before. Very reluctant to cooperate. Always busy with his blanket or shirt. Does not speak anymore; does not obey any commands.
> 31 May 1910. His body-weight falls slowly and steadily. Still fidgeting with his sheets in the same manner.
> 28 July 1910. Epileptiform seizure of 2 minutes duration.
> 1 Sept. l910. Temperature increased to 38.5 C. Rhonchi over his lung.
> 3 Oct. 1910. Death with features of pneumonia.

Johann F suffers from a series of epileptic seizures. It is possible that these may have contributed to his death from pneumonia in 1911. The description raises a number of further questions: does the right sided facial palsy represent a Todd's paresis? Are the periods of reduced responsiveness also representative of further seizures, and what about the constant fiddling with the blanket? Is that a sign of ongoing seizures manifesting as a motor automatism? Regardless of the answers to these questions we know that Johann F died only 10 months after his first witnessed seizure is recorded, and just 3 years after his initial admission to hospital and assessment by Alzheimer.

Clearly Johann F was not the first patient with dementia to experience epileptic seizures, any more than Auguste D was the first patient to suffer from dementia. Nonetheless, Alzheimer eloquently describes both cases, and many others, in a manner which establishes both the clinical features of Alzheimer's disease and the concept that these patients are at risk of developing epilepsy.

1.2.2 FURTHER REPORTS OF EPILEPSY IN AD

Despite this, the association between dementia and epilepsy continues to be debated, in terms of the clinical features and prevalence of these seizures as well as the stage of the disease in which they are most likely to occur. A literature

review of epilepsy occurring in patients with dementia forms the next chapter of this thesis.

1.2.3 EARLY ONSET AD AS A FAMILIAL EPILEPSY SYNDROME

Whilst the prevalence of epilepsy in sporadic AD, the most common form of the disease, remains disputed, there is more clarity when it comes to the early-onset, familial forms of the disease. Mutations in Presenilin-1 (PSEN1), Presenilin-2 (PSEN2) and Amyloid Precursor Protein (APP) are the three most common causes of familial AD. All three have been associated with an increased risk of epileptic seizures. In the case of disease caused by mutations of PSEN1, the risk of epilepsy is sufficiently high that it has been considered a 'genetic epilepsy syndrome' (Larner, 2011). Given that the pathophysiological mechanisms which underpin sporadic / late-onset AD overlap substantially with those responsible for the familial forms of the disease, it should not come as a surprise that this far larger group of patients are also at risk of epilepsy.

1.3 DEFINING DEMENTIA

Dementia is an umbrella term used to describe a number of different conditions, all of which lead to decline in a range of cognitive functions, usually including memory, to a degree that impairs someone's ability to complete their day-to-day activities. The prevalence of dementia increases with age such that it affects 5% of people older than 65 years of age and 20% of people over 80 (Plassman et al., 2007, Rizzi et al., 2014, Wu et al., 2017, Livingston et al., 2017). The diagnostic criteria for dementia (all sub-types) are outlined in the current diagnostic criteria for AD (McKhann et al., 2011):

> 1. Interfere with the ability to function at work or at usual activities; and
> 2. Represent a decline from previous levels of functioning and performing; and
> 3. Are not explained by delirium or major psychiatric disorder;
> 4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the

routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

These criteria describe a range of different cognitive impairments which can be present in a patient with dementia. Whilst dementia is sometimes thought of as a single clinical entity, it is in fact a collection of conditions which are epidemiologically, clinically and pathologically heterogeneous.

1.3.1 PATHOPHYSIOLOGY AND CLINICAL FEATURES OF DEMENTIA SUBTYPES

1.3.2 ALZHEIMER'S DISEASE

Epidemiology:

Alzheimer's disease is the most common form of dementia, making up around 60% of all cases. AD typically presents in the 7^{th}-9^{th} decades, although early onset familial forms can present much earlier (Hodges, 2006, Ballard et al., 2011). Moreover, evidence has shown the accumulation of the pathological changes associated with AD begins up to 2 decades before clinical symptoms manifest (Jack et al., 2013, Braak and Del Tredici, 2015). AD is equally prevalent in both

genders (Masters et al., 2015). AD has an average duration of illness of 8 to 10 years, although this varies depending on the presence of other genetic and environmental risk factors.

Clinical features:

Most commonly the onset of AD is insidious. The archetypal presentation is amnestic, with well-preserved language skills in the early stages of disease (McKhann et al., 2011, Caselli et al., 2014, Cummings, 2018). As the disease progresses other cognitive domains become affected (Perry and Hodges, 1999, Klein-Koerkamp et al., 2012, Godefroy et al., 2016).

Whilst the diagnosis of AD is most commonly clinical, the most recent guidelines for the diagnosis of AD describe a range of biomarkers which can be used to support the diagnosis (McKhann et al., 2011, Frisoni et al., 2017).

Pathology:

The pathophysiological hallmarks of AD are amyloid plaques and intraneuronal tau fibrillary tangles. The distribution of these pathological changes and their evolution as the disease progresses is described as Braak staging (Braak and Braak, 1991, Braak and Braak, 1995). This system describes pathology initially in the transentorhinal cortex before extending into the entorhinal region. Subsequently disease involves the neocortex of the fusiform and lingual gyri before spreading more widely into neocortical association areas (Braak and Del Tredici, 2015).

Alzheimer's disease is not a homogeneous entity either clinically or pathologically. Posterior cortical atrophy is an uncommon form of AD in which the focus of pathology is located in the parietal-occipital region rather than in the temporal lobes. This change in the site of pathology is inevitably associated with a change in clinical signs and symptoms. Patients with PCA report disorders of higher visual function including features of Gerstmann's syndrome (acalculia, agraphia, right/left disorientation and finger agnosia) as well as Balint's syndrome (optic ataxia, oculomotor apraxia, simultanagnosia, and environmental agnosia) (Crutch et al., 2012, Peng et al., 2016, Suarez-Gonzalez et al., 2016). PCA is regarded as a subtype of AD due to the pathological similarities that they share:

the deposition of amyloid-beta (Aβ) and tau proteins and the altered levels of these proteins when measured in CSF.

More recently, neuroinflammation in AD has been an increasing field of study. These studies have identified a number of neuroinflammatory markers in patients with AD such as activated microglia surrounding Aβ plaques and the ensuing production of interleukins. Our increasing understanding of AD as, in part, a neuroinflammatory disease, raises new possibilities for the treatment and prevention of this condition (Heneka et al., 2015, Lenart et al., 2016, Sims et al., 2017).

1.3.3 VASCULAR DEMENTIA

Epidemiology:

Often considered the second most common form of dementia, the prevalence of vascular dementia is disputed (Roman, 2004, Rizzi et al., 2014, O'Brien and Thomas, 2015). It increases with age and is associated with other vascular diseases, such as stroke, ischaemic heart disease, hypertension, and atrial fibrillation (Manso-Calderon et al., 2014). These risk factors appear to be particularly potent when present in mid-life (O'Brien and Thomas, 2015).

Phenotypically AD and vascular dementia can be very similar and are often difficult to distinguish (Roman, 2004, Smith, 2017). Many patients diagnosed with probable AD during life are found to also have evidence of vascular pathology at post-mortem (Larsson and Markus, 2018) and vice versa.

Clinical Features:

Clinically, the main difference between AD and vascular dementia is considered to be the way in which these diseases progress over time. Whilst AD has a gradual and steady decline, archetypal vascular dementia progresses in a stepwise pattern, with variable periods of relative stability followed by significant acute decline in cognitive function (O'Brien and Thomas, 2015). In addition, whilst the pattern of cognitive deterioration in AD follows a reliable pathway, because the pathology affects certain regions in a certain sequence, the patterns of impairment in vascular dementia are more variable as the areas affected by vascular pathology are themselves far more mutable (Sachdev et al., 2014).

As a result of the variable nature of the regions affected in vascular dementia, as well as the variable nature of the risk factors which have led to it, the progression of disease in these patients is harder to predict and much more heterogeneous than in AD.

Pathology:

Extensive variation is also seen in the nature of pathological changes in the brains of patients affected with vascular dementia. These changes include small vessel ischaemic lesions, cortical infarcts and cerebral haemorrhages of different sizes and with different aetiologies (Jellinger, 2008, Kalaria, 2016, Kalaria, 2018).

In post-mortem studies AD and vascular dementia pathologies are often found to co-exist (Sadowski et al., 2004, Jellinger, 2008, Chui et al., 2012). Whilst pure vascular dementia itself is relatively rare, vascular changes are seen frequently in patients with all forms of dementia and are likely to contribute to the cognitive impairment seen in these patients (Kalaria, 2018, Larsson and Markus, 2018, Scott et al., 2018, Sweeney et al., 2018).

1.3.4 DEMENTIA WITH LEWY BODIES

Epidemiology:

Dementia with Lewy Bodies (DLB) makes up from 0% to 23% of patients with dementia (Vann Jones and O'Brien, 2014). Studies have shown that it is more common in females (Walker et al., 2015). Despite making up a smaller fraction of cases of dementia overall, patients with DLB represent a disproportionately large number when it comes to hospitalised patients with dementia. This is likely due to the increased care burden and morbidity associated with this condition, leading to increased admission to secondary care, and prolonged duration of hospital stay (Vann Jones and O'Brien, 2014).

Clinical Features:

Patients with DLB present with a catalogue of cognitive symptoms which help to distinguish this type of dementia from other forms. These are reflected in the most recent DLB diagnostic guidelines (McKeith et al., 2017). The core clinical features are, 'fluctuating cognition with pronounced variations in attention and alertness,

recurrent visual hallucinations that are typically well formed and detailed and REM sleep behaviour disorder'. In addition, patients typically experience one or more of the features which we would typically recognise as cardinal features of Parkinsonism: bradykinesia, rest tremor and rigidity (Walker et al., 2015, Gomperts, 2016).

Pathology:

Pathologically, as its name suggests, DLB is marked by the presence of Lewy bodies throughout the brain. Lewy bodies are aggregates of alpha-synuclein, a presynaptic neuronal protein which has been recognised in patients with DLB and Parkinson's disease for many decades (Braak et al., 2003, Dugger et al., 2014, van der Zande et al., 2018b). The Braak pathological staging of Parkinson's disease (with or without dementia) describes Lewy body pathology starting in the dorsal motor nucleus or the intermediate reticular zone and then advancing rostrally into the brainstem, onwards into the limbic system and finally to the neocortex (Braak et al., 2003). Whilst many patients with Parkinson's disease will ultimately be diagnosed with dementia, usually because of this Lewy Body pathology, the age at which this occurs, and the duration of time from the onset of Parkinsonism to dementia is variable; the mechanisms behind this are not well understood.

Once again it is worth noting that AD and DLB frequently coexist and in many patients determining in-life which is the dominant pathology is not possible. Post-mortem studies have shown that up to 90% of DLB patients show concomitant evidence of AD pathology (Dugger et al., 2014, Howlett et al., 2015). Where this AD pathology is also present the cognitive impairment is greater and the deterioration more rapid. As with AD, recent research has focussed on the role of neuroinflammation in the pathology of DLB, as both a cause of progression and also a potential target for future therapies (Surendranathan et al., 2015).

1.3.5 FRONTOTEMPORAL DEMENTIA

Epidemiology:

After Alzheimer's disease, Frontotemporal Dementia (FTD) is the second most common form of dementia in those under 65 years of age. It affects 3-26 per 100,000 of the UK population and 70% of patients are diagnosed before the age

of 65 (Bang et al., 2015, Olney et al., 2017). Whilst it makes up a smaller proportion of dementia prevalence over that age, it still accounts for between 3% and 26% of all cases of dementia (Bang et al., 2015). There appears to be an equal risk for males and females (Rosso et al., 2003, Onyike and Diehl-Schmid, 2013), although conflicting studies have separately shown both a higher prevalence in men (Mercy et al., 2008) and in women (Bernardi et al., 2012).

Clinical Features:

Clinically and pathologically the conditions which are considered under the umbrella term of fronto-temporal dementia are a heterogeneous group. Traditionally FTD is divided into three clinical subtypes. Behavioural-variant frontotemporal dementia (BV-FTD) is the most common form, and is associated with early behavioural and executive dysfunction. Patients with Non-fluent variant primary progressive aphasia (NFV-PPA) experience progressive dysfunction of speech, grammar and output. Semantic-variant primary progressive aphasia (SV-PPA), is a progressive disorder of semantic knowledge and naming. More recent PPA classifications have divided aphasic forms of FTD into three categories - SV-PPA, non-fluent or agrammatic PPA (NFV-PPA) and logopaenic variant PPA (LV-PPA) further adding to the phenotypic heterogeneity of these patients.

Of these types, BV-FTD is the most common accounting for 50-70% of all FTD cases (Bang et al., 2015, Finger, 2016). Clinically, patients with BV-FTD may present with apathy, disinhibition or behavioural change. Whilst memory and visuospatial skills are often relatively preserved, at least in earlier stages of the disease, socially inappropriate behaviour with loss of empathy, changes in dietary intake (a ‘sweet-tooth’ and predilection for eating the same foods repeatedly) and behaviour which becomes repetitive, almost ritualistic, are more common.

Slow, halting and effortful speech are the hallmarks of NFV-PPA. Whilst aphasia can be a feature of AD, FTD is more likely to be the cause when episodic memory is relatively preserved. Patients with NFV-PPA have difficulties in comprehending complex sentences and may also show difficulties with written language production (Grossman, 2012, Lanata and Miller, 2016).

In contrast to NFV-PPA, patients with SV-PPA retain the rate and fluency of speech, but early-on show anomia and loss of comprehension for individual words. Behavioural changes are common early in the disease, especially where the right temporal lobe is involved, and increase in severity as the orbitofrontal cortex is affected (Liu et al., 2013).

The logopaenic variant of primary progressive aphasia (LV-PPA) is the most recently defined form of PPA and is an atypical presentation of AD. LV-PPA is characterised by difficulties in word retrieval and repetition of words and phrases as well as phonologic errors (Madhavan et al., 2013, Beber et al., 2014).

Pathology

Much like AD, FTD is a neurodegenerative disease in which the primary pathologic finding is the abnormal accumulation of protein(s). However, unlike AD, which is invariably due to the accumulation of beta-amyloid and tau, FTD is associated with a number of different pathological proteins: most commonly microtubulin-associated protein tau (MAPT), the TAR DNA-binding protein (TDP-43) or fused-in-sarcoma protein (FUS) (Hsiung et al., 2012, Finger, 2016, Olney et al., 2017). Studies into the pathology of LV-PPA have shown these patients to have extensive Aβ pathology involving left temporoparietal regions, leading to its characterisation as an atypical form of AD (Madhavan et al., 2013).

Recent decades have seen a great expansion in our understanding of the pathologies involved in FTD. This is particularly true of genetic risk factors for FTD where mutation in C9orf72, MAPT and GRN (progranulin) genes have been found to account for the majority of inherited cases of FTD (Olszewska et al., 2016, Zhang et al., 2016). C9orf72 is the most common of these and is also the most common genetic cause of the amyotrophic lateral sclerosis variant of motor neuron disease (Wood, 2011, Hsiung et al., 2012, Liu et al., 2013).

1.3.6 MILD COGNITIVE IMPAIRMENT

Unlike the dementia subtypes described in this chapter - which are pathologically defined, Mild Cognitive Impairment (MCI) is a neuropsychological construct that attempts to bridge the gap between normal cognitive ageing and dementia. This gap has now been further divided by the term subjective cognitive impairment

which intervenes between normal cognitive ageing and MCI. The most common presentation is amnestic (aMCI), however a range of different presentations, both clinically and pathologically, have been described (Busse et al., 2006, Bolivar and Saladie, 2016).

Epidemiology:

Given the term itself has often been disputed, it is no surprise that estimates for the prevalence of MCI in the population have varied greatly (Busse et al., 2006, Petersen et al., 2014, Eshkoor et al., 2015, Petersen, 2016, Chung et al., 2017). To reflect this difficulty, Ganguli et al report a prevalence of amnestic MCI of 2.18% in an American population over 65yrs old, a prevalence of Expanded MCI of 17.6%, but evidence of mild functional impairment (evidenced by a Clinical Dementia Rating (CDR) scale score of 0.5) in 25.4% (Ganguli et al., 2010). Similarly Busse et al., report prevalence estimates ranging from 9% to 42% depending on the MCI criteria which are used (Busse et al., 2006).

Clinical Features:

Of all of the conditions discussed in this section, Mild cognitive impairment (MCI) is the most contested and problematic. In the minds of many it is considered to be a precursor to Alzheimer's disease (Winblad et al., 2004, Albert et al., 2011, Lopez et al., 2016). However, whilst 80-90% (Eshkoor et al., 2015) of patients diagnosed with MCI will later be diagnosed with AD, this progression is not inevitable nor is the interval between these two diagnoses uniform. Moreover, studies have consistently reported that some patients diagnosed with MCI show cognitive stability over time, and in some cases even improvement (Lopez et al., 2006, Chung et al., 2017).

Much like in AD, the predominant presentation of MCI is amnestic and patients typically first report a decline in their short term memory, whilst other cognitive domains are typically well-preserved (Petersen, 2016). The dividing line between MCI and AD is sometimes unclear, in part because, in current clinical guidelines, the distinction is made by the way in which sufferers describe their symptoms and the effects this cognitive impairment has on their day-to-day functioning (Albert et al., 2011, Eshkoor et al., 2015).

Pathology:

Given the variable clinical course that MCI can take - some patients will get worse, but some will not, and some may even show improvement - it is not surprising that MCI does not have set pathological criteria as is seen in AD, DLB or even the collection of pathological findings as described in FTD (Chung et al., 2017). However, given that most patients with MCI will progress to a diagnosis of AD, these patients commonly show early changes consistent with AD pathology - namely amyloid beta deposition (Alexopoulos et al., 2013, Insel et al., 2018). These changes can be seen on dedicated amyloid imaging techniques or on measurement of CSF amyloid levels. Higher levels of amyloid burden in MCI patients are predictive of progression to AD. Patients with MCI are also more likely to have cerebral microvascular changes than cognitively normal individuals (Scott et al., 2018).

1.3.7 COMMON PATHWAYS FROM DEMENTIA TO EPILEPSY

As I have described, the term dementia refers to a series of conditions with clinical, pathological and epidemiological heterogeneity. Nonetheless, these conditions are typically considered together due to their underlying commonality - progressive cognitive impairment. Broadly speaking, these conditions all have as their final common pathological pathway degeneration of the underlying structure of the brain and premature atrophy of specific regions within it. It is because of these structural changes, and the alterations to neuronal excitability that they produce, that all can potentially lead to an increased risk of epileptic seizures (Brown et al., 2011, Garcia-Cabrero et al., 2013, Tamagnini et al., 2015b).

1.4 DEFINING EPILEPSY

1.4.1 PATHOPHYSIOLOGY OF EPILEPSY

Epileptic seizures have myriad different presentations, all related to the anatomical structures which are affected at the time of the seizure, and whether this abnormal activity remains localised or becomes more widely generalised. Underlying epileptic seizures of all types however is the abnormal synchronous firing of neurons. A diagnosis of epilepsy is confirmed when two or more unprovoked seizures occur more than 24 hours apart (Fisher et al., 2014). The

international league against epilepsy (ILAE) has recently provided updated guidance on the diagnosis of epilepsy and the classification of different seizure types (Fisher et al., 2017).

1.4.2 TEMPORAL LOBE EPILEPSY

Temporal lobe epilepsy is the most common form of adult onset focal epilepsy (Helmstaedter and Elger, 2009, Javidan, 2012, Fisher et al., 2014). Epilepsy involving the temporal lobes can result in a wide range of clinical presentations (Lanteaume et al., 2009, Pizzi et al., 2009, Blair, 2012), relating to the broad range of functions performed by temporal lobe structures and the even wider range of connections to structures outside of the temporal lobes that pass through them. This can include motor automatisms involving the hands (such as fumbling, picking or fidgeting), or mouth (swallowing, chewing, lip-smacking), vocalisations, speech / behavioural arrest, and altered consciousness (Blair, 2012). Moreover, seizures involving this region can also cause symptoms such as déjà vu, olfactory hallucinations and amnestic attacks. As this list suggests, temporal lobe seizures can be either focal onset (motor or non-motor) or focal onset with secondary generalisation, based on recent diagnostic classification (Fisher et al., 2014, Fisher et al., 2017).

1.5 DEFINING TRANSIENT EPILEPTIC AMNESIA

1.5.1 A BRIEF HISTORY OF TEA

TEA is a syndrome of temporal lobe epilepsy in which the principal manifestation of a seizure is a brief episode of amnesia during which other mental functions are predominantly or entirely preserved (Zeman et al., 1998, Butler et al., 2007). Unlike transient global amnesia (TGA), where a single episode of 2-24 hours is the norm (Bartsch and Butler, 2013), patients with TEA typically report recurrent, brief attacks which last less than one hour and often only a few minutes (Asadi-Pooya, 2014, Felician et al., 2015). Episodes typically occur at roughly monthly intervals (Butler et al., 2007), and most patients report at least some episodes on awakening.

Approximately two-thirds of patients with TEA describe other phenomena associated with temporal lobe epilepsy, including olfactory and gustatory hallucinations and oroalimentary automatisms, occurring in some or all attacks

(Butler and Zeman, 2011). Interictal routine or sleep-deprived EEGs show focal epileptiform abnormalities which help to confirm the diagnosis in around 1/3 of cases (Butler et al., 2007). Patients are usually sensitive to anticonvulsant treatment, which typically prevent the attacks completely (Butler et al., 2007, Mosbah et al., 2014). Ictal records indicate that the amnesic episodes in TEA can be either ictal or immediately post-ictal manifestations (Zeman and Butler, 2010).

1.5.2 AETIOLOGY OF TEA

Whilst our understanding of the clinical features of TEA continues to increase, the aetiological mechanism(s) behind its onset remain less well known. In the majority of patients neuroimaging investigations have been normal (Butler et al., 2007, Lapenta et al., 2014, Mosbah et al., 2014) (see below). However, in-depth volumetric studies have identified subtle atrophy in mesial temporal and orbitofrontal regions (Butler et al., 2013). EEG recordings in these patients have persistently uncovered epileptiform abnormalities in the temporal lobe, corroborating this region as the epicentre of activity in this condition (Del Felice et al., 2014, Mosbah et al., 2014, Burkholder et al., 2017), but this does not readily provide clues as to the underlying pathology in these cases. A recent case study has described TEA in a patient with NMDA receptor antibody mediated encephalitis (Savage et al., 2019b), implicating autoimmunity and inflammation as possible causative factors in TEA.

In transient global amnesia, an acute physical or psychological stress is often reported at the time of, or soon before the onset of the amnestic episode (Bartsch and Deuschl, 2010, Bartsch and Butler, 2013). The same has not been consistently reported in the case of TEA, although in their cohort of TEA patients Mosbah et al., identified a negative life event (illness, death of a relative, retirement) in 50% of patients, and a past or current history of depression in 33% (Mosbah et al., 2014).

The largest case series to have investigated TEA examined the prevalence of cardiovascular diseases in these patients; concluding that there was no compelling evidence for an increased prevalence of cardiovascular risk factors amongst TEA patients (Butler and Zeman, 2011).

1.5.3 NEUROIMAGING FINDINGS IN TEA

Although structural MRI is typically normal in TEA, imaging investigations in TEA patients have pointed to a seizure source in the medial temporal lobes (MTLs). If structural abnormalities are present, they usually lie in the MTLs. A case report of a TEA patient with frequent seizures identified high signal in the hippocampus, accompanied by hypermetabolism on PET, which resolved with successful treatment of his epilepsy (Butler and Zeman, 2008a).

A group study of patients with TEA revealed subtle, bilateral hippocampal atrophy with volume loss of 8% (Butler et al., 2009). Automated measurement of cerebral regions identified additional atrophy of perirhinal and orbitofrontal cortices (Butler et al., 2013). A functional imaging study of autobiographical recollection in patients with TEA revealed reduced activation in the posterior right parahippocampal gyrus (Milton et al., 2012). Hypometabolism of the bilateral middle frontal gyri (BA6), left medial, superior, precentral and paracentral gyri (BA6, BA31) has been identified on FDG-PET studies. Additional areas of hypometabolism within the right posterior hippocampus (BA36) and left uncus (BA28) have also been confirmed with use of a medial temporal mask (Mosbah et al., 2014).

1.5.4 NEUROPSYCHOLOGICAL FINDINGS IN TEA

Whilst the cornerstone of the TEA diagnosis is a transient period of ictal amnesia, more than two thirds of patients also report three ‘atypical’ forms of memory impairment between these episodes: accelerated long term forgetting (ALF), autobiographical (or ‘focal retrograde’) amnesia and topographical amnesia. Patients with ALF complain that information learned recently fades more rapidly than they would expect (Butler and Zeman, 2008b). On objective testing, these patients show normal acquisition of new information, performing within the normal range on standard neuropsychological tests which measure immediate recall and at an interval of 30 minutes after learning, but exhibit a more rapid rate of forgetting than usual over longer delays (Manes et al., 2005, Hoefeijzers et al., 2013, Elliott et al., 2014). Studies show loss of both the amount and the quality

of memories which begins within hours (Hoefeijzers et al., 2015) and is most pronounced during the first 24 hours of retention (Muhlert et al., 2010).

As well as a more rapid rate of forgetting for recently acquired information, these patients often report what has been described as a patchy ‘focal retrograde amnesia’. This characteristically involves a loss of memory for salient personal events, and is sometimes described as ‘holiday amnesia’ as it often comes to light when discussing these memorable, discrete, autobiographical events (such as a friend or family member’s wedding). It can extend across most or all of the lifespan, affecting memories formed well before the onset of seizures. Personal and public semantic memories are also affected but less severely (Milton et al., 2010). Describing this amnesia as ‘focal’ and ‘retrograde’ is controversial (Kopelman, 2000). Many patients with TEA have ALF, an atypical form of anterograde amnesia which would be expected to cause a cumulative amnesia for past events over time. The term ‘focal retrograde amnesia, is defensible, however , given the contrast between the relatively normal performance often demonstrated on standard measures of anterograde memory, and their marked difficulties when they contemplate remote events, often ones they could previously recall.

Patients with TEA also commonly report a topographical amnesia. This will typically manifest as difficulty in remembering familiar routes as well as in recognising familiar landmarks (Zeman et al., 2013).

1.5.5 TEA PROGNOSIS

Many patients diagnosed with TEA are initially suspected of suffering from dementia and many more are concerned that this is a possibility prior to consulting with their doctor. This is understandable given the persistent memory symptoms that these patients can experience. However, as is shown by their good performance on standard neuropsychological testing, the cognitive deficits experienced by patients with TEA are typically different to those exhibited by patients with dementia.

Despite the memory symptoms reported by these patients, recent studies have suggested that the risk of dementia is not increased by a diagnosis of TEA (Savage et al., 2016). The cognitive deficits remain stable, declining only to a

degree expected with ageing and comparable to an age matched control population without TEA (Savage et al., 2016). However, given that the prevalence and clinical features of epilepsy in patients with dementia are not conclusively known, the degree to which these two conditions can resemble each other is incompletely understood. Neuropsychological testing may prove to be a helpful discriminator between TEA and epilepsy in dementia.

1.6 MAKING THE DISTINCTION BETWEEN EPILEPSY IN DEMENTIA AND MEMORY LOSS IN EPILEPSY

When someone experiences a decline in memory, which is either noted by themselves, or by those nearest to them, the next step will likely be to make an appointment with their GP. From there, the probable next step, once it has been confirmed that a persistent problem exists, will be a referral to the memory clinic. In the UK memory clinics are designed to provide a one-stop service for the investigation, diagnosis and onwards management of memory problems, most commonly Alzheimer's disease (Van der Cammen et al., 1987, Jolley et al., 2006). Given the nature of problems caused by epileptic seizures in dementia as well as the memory problems which occur in patients with TEA, it is likely that patients with both of these conditions will be seen in this setting. With that in mind a further goal of this thesis is to aid the prompt diagnosis of these clinical presentations. This process often involves the differentiation of multiple other causes of amnesia - both transient and persistent.

1.6.1 CAUSES OF TRANSIENT AMNESIA

Work on TEA has expanded our understanding of the diagnostic possibilities among patients who present to hospital with one or several episodes of transient amnesia. The archetypal example of acute onset transient amnesia and the one of which hospital staff are most aware, is Transient Global Amnesia (TGA). It is defined by the following criteria (Fisher and Adams, 1964, Bartsch and Butler, 2013):

- Presence of an anterograde amnesia that is witnessed by an observer
- No clouding of consciousness or loss of personal identity
- Cognitive impairment limited to amnesia
- No focal neurological or epileptic signs

- No recent history of head trauma or seizures
- Resolution of symptoms within 24 h
- Mild vegetative symptoms (headache, nausea, dizziness) might be present during the acute phase

Clues to a diagnosis of TEA in contrast to TGA include the brevity of the attacks – typically less than one hour in TEA, several hours in TGA – and their frequency – typically around one/month in TEA, usually single or very infrequent in TGA. Attacks which occur on waking, prominent interictal memory difficulties and the presence of abnormalities on EEG would also make a diagnosis of TEA more likely (Lanzone et al., 2018).

In addition to these causes, a number of other diagnoses should be considered in a patient who presents with transient amnesia. These include transient ischaemic attacks and stroke (Gupta et al., 2014, Amuluru et al., 2015), head injury, infective and auto-immune encephalitis (Garcia Garcia et al., 2013, Navarro et al., 2016), and the effects of drugs and sleep inertia (Ferguson et al., 2016, Hilditch et al., 2016). Clues obtained from the history, neurological examination and appropriate investigations usually make it possible to differentiate between these causes, all of which will require different treatments and management strategies.

1.6.2 TRANSIENT AMNESIA IN DEMENTIA AND MCI

On the surface, epilepsy occurring in dementia and memory loss occurring in epilepsy (TEA) are very different: one is a progressive neurodegenerative disease in which patients experience global deficits and on top of this, experience epileptic seizures; whereas the other is a condition that is defined by transient episodes of amnesia during which other cognitive functions remain intact. However, patients experiencing epilepsy as part of their dementia report transient periods of worsened confusion and amnesia, different to their baseline cognitive impairment, and patients with TEA report some persistent memory deficits that extend beyond their seizure episodes. Moreover, recent studies comparing TEA and MCI have highlighted the potential similarities between these two conditions (Cretin et al., 2014, Del Felice et al., 2014, Holler and Trinka, 2014).

1.7 STRUCTURE OF THIS THESIS

This thesis aims to answer a number of outstanding, and clinically important, questions about epileptic seizures occurring in patients with dementia as well as TEA. In terms of the former – what is the prevalence of epilepsy in this group, who is most at risk, what do these seizures look like, and in the longer term, what effects do seizures have in this population? Chapter 2 provides a review of epilepsy in dementia. Chapter 3 reports on the prevalence and clinical features of epileptic seizures in a cohort of 144 patients recruited from a regional memory clinic. Chapter 4 presents the 12-month follow up from this cohort, to establish whether patients that experience epilepsy as a feature of their dementia progress in different ways, or more quickly than those that do not. In Chapter 5 I report on the largest cohort of TEA patients to date and compare them with previous TEA cohorts in order to establish, with greater certainty than has previously been possible, the key demographic and clinical features (both ictally and inter-ictally) of this largely under-recognized syndrome of temporal lobe epilepsy. Chapter 5 also provides a review of the literature in this field, including our own cohort in order to move towards a greater understanding of this condition. In Chapter 6 I will review one of the prominent interictal features of TEA, accelerated long-term forgetting (ALF), in order to understand the importance of this neuropsychological phenomenon in TEA as well as other conditions. In Chapter 7 I compare and contrast epilepsy in dementia and TEA, in order to establish how they can be more easily identified and differentiated in clinical practice. Both of these conditions involve similar regions, cause related problems (impairment of memory) and do so through a similar mechanism - epileptic activity.

CHAPTER TWO: A NARRATIVE REVIEW OF EPILEPSY IN DEMENTIA

2.1 INTRODUCTION

The prevalence of dementia is increasing worldwide and is expected to exceed 115 million by 2050 (World Health Organization, 2012). It is therefore not surprising that it has been recognised by the World Health Organisation (WHO) as a global health priority. It has been established for over a century that people with dementia are at risk of developing epileptic seizures. As the prevalence of dementia increases, it is inevitable that there will be a commensurate increase in the number of people who experience epileptic seizures as a feature of their illness. However, whilst it is recognised that the risk of epilepsy is increased in Alzheimer's disease (AD), the degree of this increased risk is less clear. There is also uncertainty about whether this risk is similar across all dementia subtypes or whether it is also increased in patients with mild cognitive impairment.

In this narrative review I will report broadly on the collected published evidence on epileptic seizures in dementia. I will discuss the prevalence of epilepsy in a range of dementia subtypes. In addition I will discuss the features of seizures in these conditions, their EEG findings and the proposed pathophysiology of seizures in dementia. Finally I will also review the role of anti-epileptic treatments in these conditions as well as the longer-term effects of seizures in this population.

2.2 METHODS

Multiple searches of the medical literature were performed to identify case series and case reports of epilepsy in MCI and dementia (table 2.1). Three search platforms were used: MEDLINE (from 1966), EMBASE (from 1974) and PSYCINFO (from 1806) up to September 2018. Titles and abstracts were reviewed and further hand-searching using reference lists was performed to identify further published papers. All papers where search terms appeared in the title were assessed to ensure verified diagnostic criteria had been applied to dementia diagnoses.

Reasons for exclusion included papers where epilepsy and dementia were considered separately rather than in combination, or where dementia occurred in

the setting of chronic or genetic epilepsy syndromes; as well as papers not available in the English language. A proportion of search results using all terms were conference abstracts; whilst these were reviewed, they were not included in estimates of seizure prevalence due to insufficient information regarding data acquisition and case selection being available.

Search Terms Used		Search Platform			
	Total	Medline	Embase	PsycINFO	unique
(alzheimer* or dement*) and (epilep* or seizure*)	38007	4916	11505	21586	+++
(alzheimer* and (epilep* or seizure*)	25228	2511	6280	16437	+++
("mild cognitive impairment" or MCI) and (epilep* or seizure*)	4694	139	615	3940	4481
(frontotemporal or FTD) and (epilep* or seizure*)	4134	431	1045	2658	3572
lewy and (epilep* or seizure*)	1962	83	379	1500	1835
("vascular dementia" and (epilep* or seizure*)	1440	52	166	1222	1368
"Down Syndrome" and (epilep* or seizure*)	3819	540	1150	2129	3218
(huntington* and (epilep* or seizure*)	6368	637	1900	3831	+++
"creutzfeldt-jakob disease" and (epilep* or seizure*	1444	173	745	526	1209
	abstract only				
	Total	Medline	Embase	PsycINFO	unique
(alzheimer* or dement*) and (epilep* or seizure*)	11156	3732	5781	1643	+++
(alzheimer* and (epilep* or seizure*)	5637	2013	2842	782	3309
("mild cognitive impairment" or MCI) and (epilep* or seizure*)	452	112	279	61	306
(frontotemporal or FTD) and (epilep* or seizure*)	1224	367	701	156	774
lewy and (epilep* or seizure*)	240	63	141	36	160
("vascular dementia" and (epilep* or seizure*)	161	42	95	24	108
"Down Syndrome" and (epilep* or seizure*)	835	269	437	129	493
(huntington* and (epilep* or seizure*)	1187	427	593	167	724
"creutzfeldt-jakob disease" and (epilep* or seizure*	391	128	218	45	246
	title only				
	Total	Medline	Embase	PsycINFO	unique
(alzheimer* or dement*) and (epilep* or seizure*)	803	274	389	140	453
(alzheimer* and (epilep* or seizure*)	384	123	195	66	202
("mild cognitive impairment" or MCI) and (epilep* or seizure*)	28	7	16	5	16
(frontotemporal or FTD) and (epilep* or seizure*)	47	16	23	8	23
lewy and (epilep* or seizure*)	21	7	10	4	11
("vascular dementia" and (epilep* or seizure*)	7	1	5	1	5
"Down Syndrome" and (epilep* or seizure*)	150	47	79	24	82
(huntington* and (epilep* or seizure*)	38	15	18	5	23
"creutzfeldt-jakob disease" and (epilep* or seizure*	98	37	49	12	49

Table 2.1: search terms used in literature review (+++ indicates too many results for search platform to deduplicate)

My aim in this chapter is to give an overview of the topic of epilepsy in dementia. Therefore, I chose to perform a narrative review of the literature rather than a systematic review in this instance in light of the broad scope of this narrative review and the heterogeneity of the literature identified.

2.3 RESULTS AND DISCUSSION

2.3.1 PREVALENCE OF EPILEPSY IN DEMENTIA

Few studies have looked at the prevalence of epilepsy across multiple dementia subtypes. However, where this has been done there is evidence that dementia of all forms can be associated with epileptic seizures (Hommet et al., 2008, Ashour and Abou-Hagar, 2012, Sarkis et al., 2016, Beagle et al., 2017). This risk appears to be greatest in AD: in their cohort of 77 patients with dementia and epilepsy, Sarkis et al., found that 83% had AD, 5% AD *and* vascular dementia, 1% vascular dementia, 5% Dementia with Lewy Bodies, and 5% Frontotemporal dementia (Sarkis et al., 2016).

2.3.2 PREVALENCE OF EPILEPSY IN SPORADIC AD

Despite having been described by Alzheimer himself, the risk of epileptic seizures in Alzheimer's disease is not clear. Prevalence estimates vary widely and no clear consensus has been reached. Whilst some studies have reported that the prevalence is equal to, or only mildly increased when compared to the general population (Scarmeas et al., 2009, Irizarry et al., 2012, Imfeld et al., 2013, Giorgi et al., 2016), others have identified rates of greater than 50% (Risse et al., 1990, Cabrejo et al., 2006). These studies are summarised in table 2.2.

There are several potential reasons for this variability, including the definitions of both Alzheimer's disease, and epilepsy, the means by which data is collected, and the populations which have been investigated. I will review these factors in turn and address how different studies have approached them and how this has affected their conclusions.

Author	Year of publication	Country	Number of patients	Prevalence of seizures (%)	Clinical setting / study design
Risse	1990	USA	28	64	Hospitalised male patients with advanced Alzheimer's disease. Prospective cohort study
Cabrejo	2006	France	21	57	Autopsy study from patients with APP mutation. Retrospective case series
Samson	1996	Netherlands	198	45	Population based study of patients with early-onset Alzheimer's disease
Vossel (2016)	2016	USA	33	42.4	Prospective study of patients with AD investigated using MEG and overnight EEG
Letemendia	1958	UK	17	41	Retrospective review of EEG data in patients found to have AD pathology at autopsy
Volicer	1995	USA	75	36	Hospitalised patients with probable Alzheimer's disease. Cross-sectional study
Horvath	2018	Hungary	42	24	Mixed retrospective and prospective study of patients with AD investigated with 24hr EEG
Sjogren	1952	Denmark	18	22	Pathological comparison study of patients with AD and Pick's disease
Mendez	1994	USA	446	17	Autopsy series from a brain bank. Retrospective study.
Rauramaa	2018	Finland	64	17	Clinicopathological study of patients with AD recruited to a longitudinal cohort study
Romanelli	1990	USA	44	16	Patients with mild AD. Prospective case-control study
Heyman	1987	USA	92	15	Investigations of hospitalised patients with early-onset dementia
Beagle	2017	USA	1320	13.4	Retrospective review of electronic medical records for patients who met criteria for AD
Hersdorffer	1996	USA	145	11	Population-based case-control study
Hauser	1986	USA	81	10	Autopsy study of patients with Alzheimer's disease. Retrospective
Forstl	1992	UK	56	10	Prospective clinical and neuropathological study, in patients with autopsy-proven AD
Bernardi	2010	Italy	145	9.7	Patients with probable AD in single centre. Retrospective cohort study
McAreavey	1992	UK	208	9	Hospitalised patients with dementia. Cross-sectional retrospective study

Sulkava	1982	Finalnd	71	8	Multi-biomarker analysis (including EEG) of patients with AD
Amatniek	2006	USA	233	7.75	3-centre study of patients with mild probable AD. Prospective study
Lozsadi	2006	UK	177	6.8	Outpatient dementia clinic, at time of AD diagnosis. Retrospective cohort study
Cheng	2015	Taiwan	937	4.7	Retrospective population-based study from National Health Insurance Database
Vossel (2013)	2013	USA	1024	4.1	Retrospective observational study
Rao	2009	USA	1738	3.6	Single-centre study of patients with mild dementia / MCI. Retrospective cohort study
DiFrancesco	2017	Italy	1371	2.8	Patients with pre-symptomatic dementia. Retrospective study
Giorgi	2016	Italy	1223	2.45	Key-word searching of database in a tertiary centre. Retrospective study
Bell	2011	Finland	28093	2.1	Retrospective analysis of anti-epileptic prescribing from dementia population database
Cook	2015	USA	11042	2	Data from electronic medical records. Retrospective study
Sherzai	2014	USA	3491795	1.5	Data from database of hospitalised patients. Cross-sectional study
Scarmeas	2009	USA	453	1.5	3-centre study of patients with clinical diagnosis of mild AD. Prospective cohort study
Imfield	2013	Switzerland	6932	1.3	UK-based general practice research database. Retrospective case-control analysis
Irizarry	2012	USA	3078	0.5	Patients with mild to moderate AD, previously enrolled in AD studies. Cohort study

Table 2.2: Summary of studies investigating epilepsy in AD (ranked from highest prevalence to lowest)

i. Defining Alzheimer's disease

The 2011 diagnostic guidelines for AD provide clear criteria for the diagnosis of AD, and emphasise continuing reliance on clinical decision making (McKhann et al., 2011). However, post-mortem studies have consistently shown that the clinical diagnosis is imperfect with some cases having little or no evidence of AD pathology and other cases where mixed pathologies predominate (Beach et al., 2012). In one study, the diagnostic accuracy for a clinical diagnosis of AD was shown to be 77% (Sabbagh et al., 2017). Therefore, studies need to make clear not just what diagnostic criteria have been used, but also how they have been used - for example whether CSF biomarkers have been utilised, or where biomarker imaging has been implemented. These measures have been shown to increase the diagnostic accuracy for AD to greater than 90% in terms of both sensitivity and specificity (Chiu et al., 2014, Lewczuk et al., 2018). However, the use of these biomarkers is not yet standard clinical practice around the world (Blennow et al., 2015, Villemagne et al., 2015, Olsson et al., 2016, Simonsen et al., 2017), particularly in the developing countries in which the prevalence of AD is increasing most rapidly as a result of changes in population demographics and improved life expectancy.

In keeping with advances in the use of biomarker technologies and their more widespread usage over recent decades, studies of epilepsy in dementia show significant variability as to how AD has been defined / diagnosed. Some studies outlined in table 2 use a gold-standard post-mortem diagnosis of AD (Hauser et al., 1986, Cabrejo et al., 2006, Rauramaa et al., 2018), whereas others have based the diagnosis purely on clinical features (Romanelli et al., 1990, Amatniek et al., 2006), supplemented by the use of biomarkers in more recent studies (Vossel et al., 2016, Horvath et al., 2018).

ii. Defining Epilepsy

Similarly, the definition of epilepsy is, on paper, relatively straightforward (Fisher et al., 2014). However, the diagnosis relies on recurrent episodes witnessed by a reliable informant, and clinically this can be difficult to obtain. The diagnosis does not require an EEG recording, although this test is often sought to provide supportive evidence (Sulkava, 1982). As computational approaches to EEG

analysis have become increasingly complex, so the rate at which abnormal findings are identified in the AD population has also increased. Recent studies have shown a proportion of patients with AD have epileptiform EEG changes, even where no history of seizures can be identified (Vossel et al., 2016, Horvath et al., 2018). As a result it is important that a strict and clear definition of what constitutes epilepsy is used in studies where the prevalence of epilepsy in AD is investigated. Furthermore a distinction should be made between the occurrence of a single seizure, as opposed to recurrent episodes which would be required for a diagnosis of epilepsy to be made.

Many of the studies which have identified a higher prevalence of epilepsy in the AD population have obtained more prolonged EEG recordings, or have used additional methods such as magnetoencephalography (MEG) (Vossel et al., 2016, Horvath et al., 2018). In these studies the quoted rates for the prevalence of epilepsy sometimes comprise clinically overt seizures as well as subclinical epileptiform activity.

iii. Research methods

Retrospective reviews of medical records rely on the accurate reporting and recording of information in order for it to be extracted at a later date. Evidence has suggested that the majority of epileptic seizures in patients with AD are focal in onset, and often subtle in appearance. As a result, these events may not have been reported by the patient or carer and not recorded in medical notes. It is therefore not surprising that the studies that have shown the lowest prevalence rates for seizures in the AD population have relied on a retrospective approach to data collection (Bell et al., 2011, Irizarry et al., 2012, Sherzai et al., 2014, Cheng et al., 2015, Cook et al., 2015). Moreover, the search terms used to identify epilepsy through this method vary greatly. Where some studies have just searched medical notes for ‘epilepsy’ or ‘seizure’ (Rao et al., 2009, Sherzai et al., 2014) others have used a far more extensive list of search terms (Giorgi et al., 2016, Beagle et al., 2017). The prevalence rates increase even further when the list of search terms used includes myoclonus; the incidence of which has repeatedly been shown to be increased in patients with AD (Hauser et al., 1986, Heyman et al., 1987, Beagle et al., 2017, Vossel et al., 2017).

The largest study to have investigated the prevalence of epilepsy in AD has done so through reviewing inpatient records where the primary indication for admission was epilepsy (Sherzai et al., 2014). Whilst this provides useful information regarding the rate at which patients with AD who experience seizures require hospital admission as a result of a seizure, it very likely underestimates the prevalence of seizures in this population overall. No data are available for the likelihood of a seizure occurring in a patient with dementia leading to a hospital admission.

iv. Study population

The studies which have reported the highest rates of epileptic seizures in AD have often looked at specific subpopulations of the condition in which we know the rate is most increased: in hospitalised and institutionalised patients (Risse et al., 1990, Volicer et al., 1995), in patients with advanced disease (Hauser et al., 1986, Risse et al., 1990), and in patients with early onset, autosomal dominant AD (Letemendia and Pampiglione, 1958, Samson et al., 1996, Cabrejo et al., 2006). Where prevalence rates for epilepsy in AD are quoted, the study population that has been examined for the study should be made clear. In contrast, studies where low prevalence rates have been detected have typically focussed on early or even pre-clinical cases of AD (Irizarry et al., 2012, DiFrancesco et al., 2017).

Historically, epileptic seizures have been viewed as a manifestation of advanced dementia, occurring as a consequence of extensive neurodegeneration and atrophy in these patients (Hauser et al., 1986, Heyman et al., 1987, Romanelli et al., 1990, Mendez et al., 1994, Giorgi et al., 2016). However, whilst conventional understanding has viewed epilepsy as a late-stage manifestation of AD, many more recent studies have identified seizures occurring early in the clinical disease, and in some cases even before cognitive symptoms present (Picco et al., 2011, Vossel et al., 2013, Sarkis et al., 2016).

Taking the above into account, the evidence is overwhelmingly in favour of an increased prevalence of epilepsy in AD when compared to an age-matched population without dementia (Amatniek et al., 2006, Friedman et al., 2012, Irizarry

et al., 2012, Pandis and Scarmeas, 2012, Imfeld et al., 2013, Cheng et al., 2015, Nicastro et al., 2016).

Recent studies have elucidated genetic risk factors for sporadic AD. By far the strongest and most widely studied of these is Apolipoprotein E (APOE) (van Es and van den Berg, 2009, Koffie et al., 2012, Kanekiyo et al., 2014, Bangen et al., 2016, Liu et al., 2017, Shi et al., 2017). Patients who are homozygous for the APOE4 genotype have an increased risk of developing AD. In addition, these patients often experience an earlier onset of disease and a more rapid progression of symptoms. What is less well known at this point is whether the APOE4 genotype also confers an increased risk for epileptic seizures and this would likely benefit from further research (Irizarry et al., 2012). One study in which the association between APOE4 and epilepsy in AD patients was investigated did not find a significant association (Rauramaa et al., 2018). Outside of APOE genotype, several other studies have identified other genetic loci which can increase susceptibility for AD including TREM2 and PLCG2 (Manolio et al., 2009, van Es and van den Berg, 2009, Lambert et al., 2013, De Jager et al., 2014, Escott-Price et al., 2017, Sims et al., 2017, van der Lee et al., 2018).

2.3.3 PREVALENCE OF EPILEPSY IN FAMILIAL AD

The highest risk of epilepsy in AD has been shown to exist for patients who have early onset, hereditary forms of the disease. Autosomal dominant early onset AD is caused by mutations within one of three genes: Presenilin 1 (PSEN1, 14q24.2), presenilin 2 (PSEN2, 1q42.13), amyloid precursor protein (APP, 21q21.3), or by duplication of the APP gene. Of these PSEN1 is the most common cause, in which over 185 different mutations have been reported. All four of these genetic alterations are associated with an increased prevalence of epileptic seizures (Velez-Pardo et al., 2004, Larner, 2011, Born, 2015). The highest risk of epilepsy appears to be in cases of APP duplication, but in all four instances the percentage of patients who develop seizures is greater than 40%, with an overall rate of 47.7% (Zarea et al., 2016). The lowest risk appears to be in APP mutation carriers. Zarea et al., found that seizures in this population occurred only in patients for whom 5 or more years of follow-up was available (Zarea et al., 2016).

Patients with these familial forms of AD typically experience the onset of cognitive symptoms at an earlier age and frequently experience a more rapid progression of symptoms than is seen in the sporadic AD population (Samson et al., 1996, Larner, 2011). It has also been suggested that these factors (age of onset and rate of progression) may be associated with a higher risk for the development of seizures in the population with sporadic AD (Cabrejo et al., 2006).

2.3.4 PREVALENCE OF EPILEPSY IN MCI

As approximately 80% (Del Felice et al., 2014) of patients with MCI will subsequently be diagnosed with dementia it would be expected that a proportion of these patients will also experience epileptic seizures. However, as epileptic seizures have often been thought of as a feature of dementia only when it is clinically and pathologically advanced, it could also be predicted that the prevalence of epileptic seizures in patients with MCI should be low.

Given the prevalence of mild memory symptoms in patients with epilepsy (Motamedi and Meador, 2003, Hoppe et al., 2007, Lanteaume et al., 2009) a number of studies have compared patients with epilepsy and those with MCI (Griffith et al., 2006, Holler and Trinka, 2014, Galioto et al., 2015). These studies have shown similar cognitive impairments in these two conditions, although patients with chronic epilepsy have been found to exhibit more widespread deficits than the predominantly amnestic changes seen in MCI (Griffith et al., 2006). Recent insights from the study of Transient Epileptic Amnesia, and accelerated forgetting have shown further similarities between this temporal lobe epilepsy syndrome and amnestic MCI / early AD (Rabinowicz et al., 2000, Manes et al., 2008, Cretin et al., 2014, Reiman, 2018, Weston et al., 2018)

Whilst some studies have compared the findings on memory testing in patients with MCI and those with epilepsy, there is little in the literature to describe the prevalence of new onset epilepsy in patients with MCI. One study, however, has shown a prevalence of epilepsy in an MCI population of 6.25% (Dhikav et al., 2017). This figure is higher than in some studies which have focussed on the prevalence of epilepsy in early stages of AD (Cretin et al., 2017, DiFrancesco et al., 2017). However, given increasing evidence that the risk of epilepsy in AD is increased even from the early, and even pre-clinical stages of the disease; this

figure appears in keeping with a condition which is often viewed as a precursor to a diagnosis of AD (Vossel et al., 2013, Sarkis et al., 2016). Further isolated case reports of MCI and epilepsy occurring at the same time in patients with a third comorbidity have been described, including alcohol dependence (Ishii et al., 2013) and Becker muscular dystrophy (Lerario et al., 2018).

2.3.5 PREVALENCE OF EPILEPSY IN VASCULAR DEMENTIA

Given that it is the second most common form of dementia, it is not surprising that the association between vascular dementia and epilepsy has also been investigated (Imfeld et al., 2013, Hatanpaa et al., 2014). Moreover, it has been well established that vascular injury in the brain (in the form of stroke, haemorrhage, or ischaemia) can predispose a patient to epilepsy (Berg, 2003, Camilo and Goldstein, 2004, Ryvlin et al., 2006, Lahti et al., 2017). It has also been shown that epileptic seizures occurring in the aftermath of a stroke are themselves an independent predictor for the development of dementia in these patients (Cordonnier et al., 2007).

As a result of the frequency with which vascular and AD pathologies co-occur, it is inevitably difficult to determine the relative contributions of either pathology when seizures occur in such patients. In patients with AD, the presence of vascular risk factors (such as hypertension and hyperlipidaemia) has been shown to increase the risk of epilepsy also (Amatniek et al., 2006, Bernardi et al., 2010, Cheng et al., 2015). Imfeld et al., were able to show that the risk of epilepsy is increased in both AD and vascular dementia when compared to age-matched controls without dementia. In summary, patients with AD or vascular dementia were at a much higher risk of developing seizures or epilepsy than dementia-free patients. In contrast to some studies looking at epilepsy in AD, this study did not report that younger age, younger age at dementia onset, or use of acetylcholinesterase inhibitors were associated with an altered risk of developing epilepsy. Patients with a longer duration of AD dementia (≥3 years) did have a higher risk of developing seizures, whereas in patients with vascular dementia the contrary was observed (Imfeld et al., 2013). The relative risk estimate for developing seizures or epilepsy in this study was similar in AD and vascular dementia (AD: odds ratio 6.6, vascular dementia: odds ratio 5.7). In other studies the risk of epilepsy in vascular dementia has been reported as 16.7% (Manso-

Calderon et al., 2014) and 20% (Webb et al., 2013). Webb et al., were also able to show that dementia related seizures were associated with a more rapid cognitive decline (MMSE score fall of 1.75 points/year in seizure groups vs 0.51 points/year in seizure-free group (Webb et al., 2013).

2.3.6 PREVALENCE OF EPILEPSY IN LEWY BODY DISEASE

Studies have reported a prevalence of epilepsy in DLB of between 4.7% and 14.7% (Campora et al., 2015, Beagle et al., 2017). Whilst the underlying pathological hallmarks of DLB are different to those of AD, the nature of these changes - the presence of cortical degeneration related to the deposition of abnormal proteins might be expected to increase epilepsy risk. However, studies which have investigated the relationship between DLB and epilepsy are far less common that those investigating seizures in AD (Ogunyemi et al., 2013, Campora et al., 2015, Beagle et al., 2017).

Lewy body dementia is often differentiated from Alzheimer's disease clinically, in part, by an increased rate of cognitive fluctuation from one day to the next, but also within a single day, which is not typically a feature of AD. As epileptic seizures in AD can be a cause of increased levels of fluctuation it is not surprising that papers linking DLB and epilepsy describe one as a mimic of the other, and a cause of diagnostic uncertainty (Park et al., 2014, Sun et al., 2014, Tun et al., 2017). Given the fluctuation seen in many DLB patients, seizures may often be suspected but can be more difficult to confirm (Walker et al., 2000). An increased incidence of epilepsy related myoclonus is seen in DLB in comparison to AD and FTD (Beagle et al., 2017).

2.3.7 PREVALENCE OF EPILEPSY IN FRONTOTEMPORAL DEMENTIA

If epileptic seizures in AD are related to the abnormal deposition of tau, then one might anticipate an increased incidence of epileptic seizures in frontotemporal dementia, where the pathological process in some cases is also a tauopathy (Bang et al., 2015).

Despite this there is little in the literature describing epilepsy in patients with FTD subtypes. In addition no studies have compared the prevalence rate of epilepsy

in these different pathological forms of FTD. Some case reports and small series do describe epilepsy occurring in FTD generally (Garcia-Cabrero et al., 2013, Castro-Suarez et al., 2016). One case was identified where seizures had occurred in the setting of FTD were attributed to polydipsia rather than as a consequence of the FTD pathology directly (Appleby and Tanase, 2014). Beagle et al,. compared the incidence of epileptic seizures in AD, DLB and FTD and have shown that in FTD this risk is lowest (AD 13.4%, DLB 14.7%, FTD 3.0%) (Beagle et al., 2017). In part this difference may be a result of structural differences of the tau implicated in these conditions. In AD 3- and 4-repeat (4R) helical tau filaments are the predominant form. In FTD, linear 4R tau is more commonly seen (Taniguchi-Watanabe et al., 2016, Gibbons et al., 2018). A recent study has identified that this difference results in changes in how and where the tau spreads and the effect it has on neurons (Cope et al., 2018).

2.3.8 EPILEPSY IN OTHER NEURODEGENERATIVE DISEASES

Epileptic seizures have been described in a number of other neurodegenerative diseases, in which cognitive impairment is also a feature, including Huntington's disease (HD) and sporadic Creutzfeldt - Jakob disease (CJD).

Epileptic seizures are a rare feature of HD, but as in AD are more common in patients with earlier onset of the disease, particularly juvenile onset (Schiottz-Christensen, 1969, Gambardella et al., 2001, Chuo et al., 2012, Cloud et al., 2012, Sipila et al., 2016). In these patients, the most common seizure type appears to be generalised tonic-clonic seizures, although tonic, myoclonic, and staring spells are also described (Cloud et al., 2012). In HD as in AD, there is a correlation between age at onset and the rate of cognitive decline which is likely a factor in the prevalence of epilepsy in both conditions. Why this is the case is not clear, although in both conditions earlier age of onset is associated with a more rapid accumulation of the pathological hallmarks of these diseases: due to an increased likelihood that younger patients have a genetic form of AD, and due to a higher CAG-repeat count in younger HD patients as a result of anticipation.

A variety of seizure presentations have been reported in CJD including non-convulsive and generalised status epilepticus, as well as focal motor seizures (Rossetti and Dunand, 2007, Ogawa et al., 2011, Ng et al., 2014, Alobaidy et al.,

2016, Mahboob et al., 2018, Miyake et al., 2018). Whilst the cognitive changes seen in prion diseases such as CJD are typically more extensive and rapidly progressive than those of AD, the pathological features of both conditions have been shown to be associated with increased neuronal hyperexcitability (see below) and in both this is considered to be the underlying mechanism behind epileptic seizures in these patients (Bertani et al., 2017).

Whilst not a neurodegenerative condition, Down's syndrome is worth mentioning here given that dementia and epilepsy so commonly occur in this condition (Lott et al., 2012, Barca et al., 2014, Aller-Alvarez et al., 2017). Moreover, Down's syndrome is caused by trisomy of chromosome 21, which is the location of the gene for APP, one of the commonest causes (both through duplication and mutation) of familial AD (Collacott, 1993, Lott et al., 2012, Gholipour et al., 2017). Almost 40% of those with Down's syndrome who are 60 years of age or older are diagnosed with dementia (Hanney et al., 2012) . There is a bimodal distribution in the age of seizure onset, with one peak in the first decade and a second occurring in the 5th and 6th decades, likely a result of neurodegenerative processes. Seizure features in this population typically include both generalised and focal epilepsies as well as late-onset myoclonic epilepsy, and are associated with an increased incidence of dementia and earlier mortality than in those without epilepsy.

2.3.9 EEG IN DEMENTIA

Whilst recent years have seen an increase in the clinical utility of biomarkers in the diagnosis of dementia, the use of EEG has not become a routine element of the diagnostic process. Nonetheless numerous studies have looked at the use of EEG in different dementia subtypes in an attempt to investigate whether it can be used to discriminate between them (Bonanni et al., 2016, van der Zande et al., 2018a). These studies have identified differences between EEG recordings in AD vs DLB patients, even when mixed pathology is present. As described by van der Zande et al., these differences included a higher prevalence of diffuse abnormalities (consisting of posterior dominant frequency below 8 Hz, diffuse slow wave activity or decreased reactivity of the background pattern to eye opening) in DLB/AD+ and DLB/AD- vs AD patients as well as a significant

difference between both DLB groups and AD for global alpha band Phase Lag Index (a measure of functional connectivity) (van der Zande et al., 2018a).

In addition, the use of EEG to investigate the relationship between Alzheimer's disease and epilepsy has also increased. In part this is a result of findings from animal studies of AD pathology, in which epileptic seizures were identified (Palop et al., 2007, Palop and Mucke, 2009, Ziyatdinova et al., 2011, Born et al., 2014, Ziyatdinova et al., 2016). These studies, particularly focussed on APP transgenic mice, have shown EEG signatures of neuronal hyperexcitability in the presence of Amyloid-beta (Aβ) deposition in mice that exhibit clinical seizures as well as those that do not (Booth et al., 2016, Ziyatdinova et al., 2016). These findings have proven harder to replicate in human studies, as a consequence of EEG changes which are evident in the ageing brain and make EEG evaluation more difficult in this population, and also because the animal studies in which epileptiform activity was identified utilised deep EEG electrode placement into mesial temporal lobe structures which are harder to record when surface EEG placement is used.

To overcome the mesial temporal lobe's resistance to interrogation, extended EEG recording - either in the form of ambulatory EEG or through sleep EEG - has emerged as a more consistent means of identifying abnormalities (Vossel et al., 2016, Horvath et al., 2017). However, longer duration EEG recording, particularly in the hospital setting does pose significant practical challenges for patients with dementia (Horvath et al., 2016). Studies that have adopted this approach have identified a number of different findings which have increased our understanding of this area. It has been shown that a 1 hour EEG recording during night-time sleep has the same sensitivity for the identification of epileptiform discharges as at least 8 hours of awake daytime recording (Horvath et al., 2017). Where abnormal findings are identified, these most commonly include increased slow wave activity, across temporal regions in the early stages, and more diffusely later on (Visser et al., 1987, Rice et al., 1990, Malek et al., 2017). These changes are in keeping with the progression and location of pathology in advancing AD. Moreover, increased delta and theta rhythms over the temporal regions have been shown to correlate with cognitive performance, to differentiate patients with dementia from controls, and to predict progression in MCI (Prichep, 2007, Kroigard et al., 2018).

More recently, more complex mathematical modelling techniques, including graph theory, have been applied to EEG recording in patients with dementia in an attempt to identify electrophysiological signatures that may enable the use of EEG as a non-invasive means of early diagnosis in these conditions and improve our understanding of their pathophysiology (Stam et al., 2009, Vecchio et al., 2016, Smailovic et al., 2018, Weiler et al., 2018). Results from this work have shown changes in cortical network topology, with reduced network efficiency and reduced connectivity in prodromal and mild dementia due to AD (Vecchio et al., 2016, Franciotti et al., 2018).

More complex or invasive methods of EEG recording, such as MEG and foramen ovale electrode placement have also been shown to identify an increased rate of epileptiform abnormalities and in some cases silent seizures in AD patients (Lam et al., 2017).

It has been shown that these complex EEG biomarkers, such as functional network efficiency and the functional brain connectome, can be predictive of progression to AD in patients with MCI (Poil et al., 2013, Wang et al., 2013, Babiloni et al., 2018). Moreover, EEG abnormalities including delta and theta slowing involving the temporal lobes, have also been shown to be associated with an earlier age of onset and cognitive decline in patients with MCI and AD (Prichep, 2007, Vossel et al., 2013).

Studies looking at EEG in DLB have reported extensive generalised slowing and a higher prevalence of frontal intermittent rhythmic delta activity (FIRDA) (Calzetti et al., 2002, Roks et al., 2008, van der Zande et al., 2018a). In 2016, Cromarty et al reviewed the evidence for a range of neurophysiological techniques in order to identify biomarkers for DLB (Cromarty et al., 2016), including MEG and transcranial magnetic stimulation (TMS) as well as more conventional EEG methods. As before, an increase in posterior slow-wave activity was found to differentiate DLB from both controls and patients with AD, a finding which is also supported by evidence from a MEG study (Bosboom et al., 2009). They conclude that further research is indicated in order to maximise the diagnostic specificity and sensitivity of these techniques.

FIRDA is also seen in early stages of sporadic CJD, but more pronounced changes such as periodic sharp wave complexes (PSWC) become more common as the disease progresses. PSWC, either lateralised or generalised, have been identified in the majority of CJD patients during the course of their disease (Malek et al., 2017).

EEG changes have been reported in patients with Frontotemporal lobar degeneration and have been shown to correlate with the degree of impairment in these patients (Chan et al., 2004). EEG abnormalities in these patients include disruption of the alpha rhythm and slow wave changes.

2.3.10 SEIZURE SEMIOLOGY IN DEMENTIA

In his 1911 account of Johann F, Alzheimer described an epileptiform seizure, lasting a few minutes, with twitching of the face and a facial palsy that was still the following day. More recent literature has shown that patients with dementia can experience a broad range of seizures, some obvious and self-evident, some more subtle, and as we have seen, some subclinical epileptiform activity which can only be identified on prolonged EEG recordings. The findings of studies which have looked at seizure semiology in AD are summarised in Table 2.3. These studies reflect an evolution in our understanding of seizures in this population, with non-convulsive and non-motor seizures being increasingly recognised in more recent studies (Vossel et al., 2013, Horvath et al., 2018). However, even the earliest study described in this table recognizes the difficulty in identifying and recording partial seizures in this population (Hauser et al., 1986).

Author	Year	Seizure Semiology
Hauser	1986	100% had generalized convulsions
Heyman	1987	71% recurrent, severe generalized seizures; 29% had myoclonus, 75% of whom developed major motor seizures during follow-up
Mendez	1994	generalized tonic-clonic seizures in 90%
Scarmeas	2009	"changes in level of attention" in 100%, "whole body convulsion” in 86%, "clinical semiology of lateralised findings" in 29%
Bernardi	2010	93% complex partial seizures, 7% generalised attacks: For most patients with partial complex seizures the informant reported initial motor signs including head version or oral automatisms and loss of consciousness, followed by tonic-clonic seizures

Vossel	2013	complex partial seizures in 47%, 36% apparent generalised seizures, 17% simple partial seizure. 55% had only nonconvulsive seizures (jamais vu, deja vu, sensory phenomena, psychic phenomena, speech/behavioural arrest, aphasia, and amnestic spells)
Horvath	2018	generalized tonic-clonic seizures in 11% and focal onset seizures with impaired awareness in 72%. Fifty-five percent of seizures were non-motor

(Table 2.3: Seizure semiology in AD)

Whilst seizure prevalence in differing dementia subtypes appears to vary, whether the same is true of the seizure semiology is less clear, although the seizure features in these patients do not seem to be specific to a particular neurodegenerative syndrome (Beagle et al., 2017). Moreover the range of seizure features seen in this population is in keeping with the seizure semiology seen in patients with temporal lobe epilepsy without a history of pre-existing dementia (Fogarasi et al., 2007).

The reported seizure semiology in dementia has been shown to depend, to a degree, on the means of data acquisition. In studies where retrospective data collection has been used, generalised seizures appear more common, whereas prospective studies are more likely to identify seizure types which are more subtle. Recent literature has shown that focal onset seizures, with loss of consciousness, appear to be the most common seizure type (Sarkis et al., 2016). Difficulty in recognising epileptic seizures is a recurrent problem and it has been noted that complex partial seizures, presenting as brief moments of altered awareness, staring, behavioural arrest, or transiently increased confusion, can easily be confused for worsening or fluctuation of the dementing illness as opposed to epileptic seizures (Mendez and Lim, 2003). Transient amnestic spells, déjà vu, jamais vu and unexplained emotions are all reported seizure features in this population and pose challenges in identification in patients with dementia (Rabinowicz et al., 2000, Cretin et al., 2012, Cretin et al., 2014, Vossel et al., 2017). Many of these seizure features are in keeping with the primary sites of pathology in patients with AD, being representative of focal seizures originating in the mesial temporal lobe / hippocampus.

Myoclonus, quick, involuntary muscle jerks, have myriad causes but can be a feature of epilepsy. Studies have shown that epileptic myoclonus is a common feature (and one which is often overlooked) in patients with dementia (Risse et

al., 1990, d'Orsi and Specchio, 2014, Beagle et al., 2017). In patients with AD, myoclonus has been shown to be both cortical and subcortical in generation, most commonly affecting the fingers. Myoclonus appears to be more common in familial forms of AD than in later onset sporadic forms, and the prevalence has been shown to increase as the disease progresses (Hallett and Wilkins, 1986, Ugawa et al., 1987, Eberhardt and Topka, 2017).

2.3.11 PATHOPHYSIOLOGY OF SEIZURES IN DEMENTIA

To better understand the risk of epilepsy in dementia, a clear pathological mechanism should be identified that connects these two conditions. This has been the focus of increased interest over recent years, following the identification of epileptic seizures in transgenic mice which exhibit AD pathology (Palop et al., 2007, Palop and Mucke, 2009). A number of different murine models have been used, and whilst many of these display similar pathologic features to each other, and to those seen in human patients with AD, there are also differences. Whilst this could be viewed as a drawback (mouse models do not perfectly replicate human AD and therefore findings from these studies should be interpreted with caution), there are also benefits which add to our understanding of the precise pathologic mechanisms underlying the relationship between epilepsy and dementia (Yan et al., 2012). For example, some of these models exhibit only Aβ pathology, and not tau, whereas others demonstrate tau but not Aβ, extending our understanding of how each of these proteins contributes to the clinical findings of AD.

Palop showed that one of these models, hAPP-J20, experienced epileptic seizures and that this resulted in a more rapid decline in their performance on cognitive tasks when compared to their litter mates. This study suggests that chronic exposure to high levels of Aβ sensitizes at least some neuronal networks to overexcitation, thereby precipitating seizures. Moreover it was also found that this neuronal overexcitation led to compensatory remodelling of inhibitory circuits which ‘end up constraining the functional agility of specific excitatory circuits’ and consequently adding to the cognitive impairments in these animals (Palop et al., 2007, Noebels, 2011).

Numerous studies have further investigated the potential for Aβ deposition in the setting of transgenic mouse models of AD to lead to neuronal hyperexcitability and epileptic seizures (Chan et al., 2015, Stargardt et al., 2015, Tamagnini et al., 2015b, Tamagnini et al., 2015a). This amyloidopathy has been shown to cause alterations in intrinsic excitability leading to persistent hyperexcitability and potential recurrent epileptic seizures (Gurevicius et al., 2013, Tamagnini et al., 2015b). It has been suggested that this hyperexcitability may at first be a compensatory mechanism to counter excessive levels of Aβ deposition during early, pre-clinical stages of AD, but that once a threshold level is reached and deposition exceeds the capacity for clearance, synaptic dysfunction occurs leading to disease progression (Stargardt et al., 2015), and neuronal loss (Scharfman, 2012). Evidence for this theory comes again from animal models, where environmental enrichment has been shown to lead to increased synaptic transmission and plasticity, and as a consequence of this, increased Aβ clearance (Eckert and Abraham, 2013, Stargardt et al., 2015). Importantly it has been shown that Aβ disrupts neural circuits at early stages of AD disease models, independent of, and prior to, Aβ plaque formation (Hsia et al., 1999).

In contrast, it has also been shown that Aβ oligomers can reduce synaptic transmission, both at pre- and post-synaptic levels, thereby exerting the cognitive effects of AD through reduction in synaptic plasticity (Sepulveda et al., 2009). It has been posited that this effect of Aβ to keep neuronal excitation in check, may in fact block epileptiform activity in hippocampal neurons.

Whilst the majority of studies looking at the interplay of epilepsy and dementia have focussed on the role of Aβ in this relationship, some studies have looked at how the other pathological hallmark of AD, phosphorylated tau, could also play a role. It has been shown that tau is released as a product of cell death and can accumulate as a result of this. In addition, tau can also cross synapses, a process known as trans-synaptic spread, which is facilitated by neuronal hyperexcitability (Pooler et al., 2013). It has been suggested that the neuronal excitability seen in the brains of patients with AD leads to an accelerated propagation of tau pathology, and that this process is further accelerated in the presence of epilepsy (Lewis and Dickson, 2016). A relationship between excess tau pathology and cognitive decline has also been shown in a study of patients with temporal lobe epilepsy (Tai et al., 2016). In this study of temporal lobe resections in patients

with refractory epilepsy, more extensive tauopathy was correlated with accelerated cognitive decline in verbal learning and Graded Naming Test scores. In some of these patients the distribution of tau pathology was similar to that seen in patients with AD

2.3.12 PROGNOSIS OF SEIZURES IN DEMENTIA

There is evidence that the presence of seizures in dementia is related to an increased rate of cognitive decline in these patients. This includes a decline in language ability as well as other indicators of disease severity including overall executive function (Volicer et al., 1995, Vossel et al., 2016). However, other studies have shown that epilepsy in this population does not affect the course or duration of disease (McAreavey et al., 1992, Samson et al., 1996, Amatniek et al., 2006).

Epileptic seizures occurring in the setting of MCI are also a predictor of progression to AD (Babiloni et al., 2018).

2.3.13 TREATMENT OF SEIZURES IN DEMENTIA

There are no randomised controlled trials comparing the efficacy and tolerability of different anti-epileptic treatments in patients with dementia.

The treatment of seizures in dementia is inevitably complicated by the nature of the patients in whom this combination occurs. Older patients with dementia typically have multiple comorbidities and are already coping with the polypharmacy associated with their conditions, on top of which other age related physiological and pharmacokinetic changes such as reduced renal function and impaired hepatic clearance mechanisms can make the decision to initiate a new medication for the management of epilepsy a harder one than it would otherwise be (Mendez and Lim, 2003, Carter et al., 2007, Sivaraaman and Vajjala, 2015). Monitoring these changes and their effects can be especially difficult in patients with dementia.

Whilst some patients with dementia will experience many seizures, leading to a diagnosis of epilepsy, in others only a single seizure occurs, and therefore anti-seizure medication may not be indicated. In a further proportion seizures may be very infrequent and therefore on balance the decision is often made not to initiate

treatment (Mendez and Lim, 2003). Evidence suggests that there is an increased risk of seizure recurrence in younger patients, those in more advanced stages of dementia and those in whom an EEG identifies grossly epileptiform activity and the presence of these features will influence decisions surrounding the use of anti-convulsant medications. The risk of recurrent seizures increases further comorbidities are also present: such as stroke, or Down syndrome (trisomy 21) (Menendez, 2005).

In 2016 the treatment of epilepsy in patients with Alzheimer's disease was the topic of a Cochrane review (Liu et al., 2016). This review concludes that no significant difference exists in terms of seizure freedom between two of the most commonly used medications - Levetiracetam and Lamotrigine, and that whilst Levetiracetam may improve cognition but worsen mood, Lamotrigine could worsen cognition and improve mood. Ultimately the review notes that the level of evidence in this area is very low and further studies are required to determine how effective and well tolerated epilepsy treatments are in patients with AD. Broadly speaking, newer anti-epileptic drugs appear to be better tolerated and less prone to side-effects than older medications. Sodium valproate, one of the most widely used drugs in the treatment of epilepsy, has been shown to increase the risk of agitation in patients with dementia (Baillon et al., 2018).

Several studies have shown that the use of anti-epileptic medications can improve cognitive performance in mouse models of dementia (Horvath et al., 2016). However, many of these studies report on relatively short-term use of these medications as opposed to the more enduring use which would be required in older adult human populations (Qing et al., 2008, Ziyatdinova et al., 2011, Sanchez et al., 2012, Devi and Ohno, 2013); therefore limiting how much can be inferred from these findings. Nonetheless where the use of medication in patients with dementia has been investigated there is evidence that seizure control is achieved relatively easily, often with low doses of medication (Sarkis et al., 2016). The use of sodium valproate has been shown to reduce Aβ production in mouse models of AD (Qing et al., 2008) and subsequently provide protection against neuronal loss (Long et al., 2013). Levetiracetam treatment has also been shown to reduce epileptiform activity and lead to some cognitive improvements when used in similar mouse studies (Sanchez et al., 2012, Devi and Ohno, 2013, Musaeus et al., 2017). In addition, there is evidence showing a cognitive benefit

in human studies using Levetiracetam in patients with AD (Belcastro et al., 2007, Cumbo and Ligori, 2010, Bakker et al., 2012, Bakker et al., 2015).

Further studies of the sustained use of antiepileptic treatment in patients with AD are indicated. Given that a small proportion of patients with AD experience clinically evident seizures, but that a larger proportion exhibit epileptiform activity on prolonged EEG recording, patient selection for these studies is clearly a complex issue. Moreover, given that extensive neuronal hyper-excitability has been shown to increase the deposition of Aβ it may be possible that antiepileptic treatments can have a beneficial effect on patients with AD even in the absence of clearly epileptiform changes on EEG recordings.

2.4 CONCLUSIONS

Extensive evidence shows an increased risk of epilepsy in all forms of dementia, but particularly in Alzheimer's disease, in which the risk of epilepsy reported in the literature varies greatly, and has been found in some studies to be over 50% (Risse et al., 1990, Cabrejo et al., 2006). Recent years have seen an expansion in our understanding of the underlying mechanisms which may lead to seizures in these patients and point towards a bidirectional relationship in which AD pathology increases the risk of seizures which are in turn associated with an increase in the rate at which AD pathology accumulates and the anatomical regions where it aggregates.

However, numerous questions remain, not least for the clinician whose job it is to diagnose and manage patients with dementia. What should we tell patients about the overall risk of epilepsy in dementia, and for their risk in particular; are there reliable ways that this can be identified; and how do epileptic seizures affect their prognosis?

CHAPTER THREE: THE PREVALENCE AND CLINICAL FEATURES OF EPILEPTIC SEIZURES IN A MEMORY CLINIC POPULATION

3.1 INTRODUCTION

Patients with dementia are at risk of developing epileptic seizures (Amatniek et al., 2006, Lozsadi and Larner, 2006, Rao et al., 2009, Scarmeas et al., 2009, Sen et al., 2018). This was reported by Alzheimer himself in his description of Johann F in 1911 (Moller and Graeber, 1998). However, the extent to which this risk is increased has been disputed and remains unclear (Horvath et al., 2016). Estimates of the prevalence of epilepsy in patients with Alzheimer's disease range from 0.5% (Irizarry et al., 2012) to 64% (Risse et al., 1990). Moreover, whilst conventional wisdom has considered epilepsy to be a feature of advanced disease in these patients (Cheng et al., 2015), more recent evidence has reported patients developing epilepsy early in the course of clinical disease (Vossel et al., 2013) and in some cases even before a diagnosis is made (Sarkis et al., 2016). In addition, studies have suggested that epileptic seizures may contribute to and even accelerate the cognitive decline seen in these patients (Vossel et al., 2016). Finally, whilst several studies have looked at the prevalence of epileptic seizures in Alzheimer's disease, these studies have typically focussed on tertiary specialist centres, with a higher proportion of patients with early onset Alzheimer's disease, in which the increased prevalence of epileptic seizures is well-described (Cabrejo et al., 2006, Larner, 2011), and complex cases, in which features such as seizures, are again likely to be more common (Giorgi et al., 2016). I aimed to use the memory clinic, the most common setting for dementia diagnosis in the UK, as the pool for our participants, in order to provide a real-world and clinically relevant estimate for the prevalence of epilepsy in this population.

In the UK, the diagnosis of dementia, or of mild cognitive impairment (MCI) is usually made at a memory clinic in secondary care. These clinics have been established throughout the UK following a governmental initiative, and provide a rapid, 'one-stop', method of assessment for patients with memory disorders (Philpot and Levy, 1987, Jolley et al., 2006) . Patients, typically referred by their general practitioner (GP), attend alongside a reliable informant (most commonly

their spouse) and undergo assessment by several members of the mental health team, yielding a cognitive profile and diagnostic formulation.

In the Presentation of Epileptic Seizures in Dementia (PrESIDe) study I investigate the prevalence and characteristics of epilepsy in a cohort of memory clinic patients. While this does not strictly provide a community-based sample, the National Institute for Health and Care Excellence (NICE) recommends referral to the memory clinic for all patients in whom dementia is suspected (NICE, 2017). As the memory clinic is the first contact patients will have with a specialist clinician in this field, determining the prevalence of epilepsy in this population is of great clinical value.

Given that seizures occurring in the context of dementia can be subtle, and are probably underreported (Sarkis et al., 2016, Horvath et al., 2018), I designed a proforma to elicit symptoms suggestive of seizures for use in interviews with patients and informants (appendix 1). I used accepted current diagnostic criteria to confirm dementia diagnoses. The main aims of our study were therefore to establish the prevalence of epilepsy in a relatively unselected group of patients with MCI/early dementia and to determine their clinical features. I compared the prevalence of epilepsy in the patient group with the prevalence assessed using the same approach in a group of healthy participants matched for age, sex and years of education. Our findings underline current uncertainties regarding the appropriate management of epilepsy occurring in early dementia.

3.2 MATERIALS AND METHODS

3.2.1 PARTICIPANTS

144 patients and 80 age- and gender-matched control participants were recruited to the study. The size of these samples was determined using a power calculation (α level P=0.05, power 80%) in order to detect a 5% difference in the prevalence of epilepsy between the dementia and MCI population vs the control population. Patients were identified through their attendance at the memory clinic in Exeter, Devon, UK, and were considered eligible for inclusion if a diagnosis of MCI or dementia (of any kind) was made at their memory clinic assessment. All eligible patients who had attended the memory clinic over an 18 month period (January 2016 - June 2017) and who had consented to take part in research were

approached. Patients from the total memory clinic population were excluded if a diagnosis other than dementia or MCI had been made (for example subjective memory impairment), where consent to be contacted was not provided, or where a reliable informant was not available to accompany the participant for the interview. The control group was identified with the help of the Exeter 10,000 study. The Exeter 10,000 (EXTEND)/Peninsula Research Bank (PRB) was set up to collect and store genetic, biological, clinical and lifestyle information on 10,000 adult individuals living in Exeter. This has established a sampling framework from which individuals can be selected, on the basis of (genetic/non) genetic predisposition/protection factors, to be invited for further research into the mechanisms of health and common disease. It is managed through the NIJR Exeter Clinical Research Facility (Exeter CRF) https://crf.exeter.ac.uk/web/content/exeter-10000-peninsula-research-bank. In the control group there was no reported history of cognitive impairment, and these patients had not previously been seen by the memory clinic. A preceding history of epilepsy was not an exclusion criterion. I used regional postcodes as a surrogate marker of socioeconomic status between the control and study populations.

3.2.2 CLINICAL INTERVIEW

I interviewed patients with a diagnosis of MCI or dementia at their own home, in the company of a reliable informant, who was subsequently seen independently. The interview was guided by a standardised proforma designed for this purpose (appendix1). Validated diagnostic criteria (Albert et al., 2011, McKhann et al., 2011, Sachdev et al., 2014, McKeith et al., 2017) were used to specify the clinical dementia diagnosis.

Background demographic data were gathered. Subsequent questioning focussed on three main areas 1) past medical and family history 2) history of dementia / MCI symptoms and 3) presence of clinical features suggestive of epilepsy.

Cognitive testing using the Addenbrooke's cognitive examination – version III (ACE-III) (Hsieh et al., 2013) was performed (appendix2). This examination had been performed on all participants at the time of their memory clinic appointment. It was repeated at the time of initial study assessment after a mean delay of 235.5

days (SD 106.5 days). Diagnostic criteria state that individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers, although these ranges are for guidance rather than cut-off scores (Albert et al., 2011). For this study I chose to use the memory component of the ACE-III for this purpose. In keeping with diagnostic criteria MCI was defined as a score >1 standard deviation below the mean in this test, but with preservation of independence in functional abilities. Informants were asked to complete two further questionnaires: the Cambridge Behavioural Inventory - Revised (CBI-R) (appendix3) and the Clinical Dementia Rating (CDR) (appendix 4). These validated questionnaires were chosen to provide an additional insight into the impact of the cognitive impairments experienced by our study participants, as witnessed by those closest to them (Morris, 1997, O'Bryant et al., 2008). The CBI-R has been shown to effectively discriminate between different dementia subtypes (Wear et al., 2008). The CDR- sum of boxes (CDR-SOB) is a summated score which incorporates the different domains examined in this questionnaire.

Expected seizure phenotypes in this population were identified from reviewing previous literature comprising generalised tonic-clonic seizures, behavioural arrest, amnesia on waking, olfactory hallucinations, abnormal movements including myoclonus, and the presence of a clear aura preceding the abnormal episode (Vossel et al., 2013, Vossel et al., 2017). Patients were categorised in to one of three groups: epilepsy probable, epilepsy possible, no clinical evidence of epilepsy (NCEE). The criteria for this categorisation are outlined in table 3.1.

Epilepsy Probable	At least 2 stereotyped episodes suggestive of epilepsy witnessed by a reliable informant
Epilepsy Possible	Single witnessed episode suggestive of epilepsy, or at least 2 episodes but not both reliably witnessed
No Clinical Evidence of Epilepsy	No suspicious episodes reported by patient or informant
Seizure features: altered responsiveness, speech / behavioural arrest, oral/pharyngeal automatism, olfactory / gustatory aura, involuntary movements suggesting focal motor seizure, other sensory phenomena (including hallucination), amnesia on waking	

Table 3.1: seizure group criteria

Cognitive performance of the control group was assessed using the ACE-III, and the same seizure identification questions were asked to each control participant and a reliable informant to determine the prevalence of epilepsy. On average, the duration of interviews was approximately 2 hours. I performed all interviews for patients and controls in their own home setting.

3.2.3 STATISTICAL ANALYSIS

I performed between-group analysis of demographic features, cognitive test performance and informant completed questionnaire scores using independent sample t-tests. Chi-square testing was performed to compare proportions between participants and controls. Multiple linear regression analysis was performed to assess the relationship between dependent and independent variables. A Bonferroni correction was made to adjust for multiple comparisons. Statistical significance was judged as any p-value <0.05. IBM SPSS statistics 22.0 and STATA were used to perform data analysis.

Ethical approval for this project was awarded through the Integrated Research Application System (IRAS) and provided by the London – Bromley Research Ethics Committee.

3.3 RESULTS

3.3.1 DEMOGRAPHIC CHARACTERISTICS

From a pool of 300 memory clinic patients who met eligibility criteria for study involvement, I recruited 144 patients to the study: 53% male, 47% female. The age at onset of memory symptoms varied from 51yrs to 91yrs (mean 75.10, SD 7.07). The age at memory clinic assessment ranged from 57yrs to 94yrs (mean 77.98, SD 6.75).The demographic features of the memory clinic sample are similar to the memory clinic population in whom a diagnosis of dementia or MCI was made (n=300) from which they were recruited: age - mean 76.82 (SD 9.94), 52% male, 48% female. The standard deviation for the memory clinic population is greater than the study population. This is a result of younger patients being

more likely to be excluded (no diagnosis of dementia or MCI made) and older patients less likely to consent to study participation when contacted. Of the 156 patients who were initially contacted but did not take part in the study, 102 (65.38%) declined involvement. 43 (27.56%) patients did not respond to follow-up telephone calls to discuss their potential involvement. 11 (7.05%) patients were not appropriate for inclusion as a result of not being able to name an appropriate reliable informant to take part in the study.

The control group (n= 80) was well-matched for gender (55% male, 45% female) and age (mean= 77.39, SD = 4.31) with the patient group. The size of the control group was determined through a calculation in order to detect a statistically significant difference (α level P=0.05, power 80%). There was no significant difference between the control group and the study group in terms of total years of education. The only significant difference between the study group and the control population was, as expected, cognitive function as measured by the ACE-III examination (table 3.2).

	Age (mean, SD)	**Gender (M:F)**	**ACE-III (Mean, SD)**
memory clinic sample (n=300)	76.82, 9.94	156:144	73.97, 14.21
PrESIDe total (n=144)	77.98, 6.75	76:68	74.16, 11.94
No clinical evidence of Epilepsy (n=107)	77.74, 6.65	54:53	74.39, 12.31
Epilepsy Possible (n=19)	79.11, 8.39	12:07	72.42, 11.81
Epilepsy Probable (n=18)	78.25, 5.36	10:08	74.61 10.13
Control group (n=80)	77.39, 4.31	44:36	95.24, 2.37

Table 3.2: demographic and ACE-III features in seizure categories

The memory clinic cohort and the control group were also compared in terms of medical comorbidities. No significant differences between these groups were identified (table 3.3).

	Total PrESIDe (n=144)	NCEE (n=107)	Poss+Prob (n=37)	Control (n=80)	Total PrESIDe v Control
Hypertension	34	29.9	45.9	37.5	P=0.600
Atrial Fibrillation	14.6	14	16.2	13.75	P=0.862
Stroke	9.7	8.4	13.5	7.5	P=0.581
Transient Ischaemic Attack	6.9	5.6	10.8	10	P=0.414
Myocardial Infarction	6.3	6.5	5.4	11.25	P=0.193
Migraine	3.5	2.8	5.4	3.75	P=0.923
Depression	9	7.5	13.5	8.75	P=0.950

Table 3.3: comparing percentage of patients with common conditions in study groups

3.3.2 DIAGNOSIS

102 participants were diagnosed with Alzheimer's disease. Of the remainder, 20 received a diagnosis of MCI, 16 a diagnosis of vascular dementia, 4 dementia with Lewy bodies, 1 FTD and 1 posterior cortical atrophy (PCA) variant of AD. At the time of memory clinic assessment the duration of memory symptoms reported by the patients ranged from 6 months to 120 months (mean 31.9, SD 15.4).

3.3.3 COGNITIVE TESTING

A decline in ACE-III scores was seen in all three seizure categories between their initial memory clinic assessment and study interview (figure 3.1). The difference between these two time points was significant only in the no clinical evidence of epilepsy group. The difference in the size of decline between the different groups was not significant. One participant (EX035) had a mini-mental state examination (MMSE) performed at the time of their memory clinic appointment, instead of an ACE-III. This participant has therefore been excluded from comparisons of cognitive test scores.

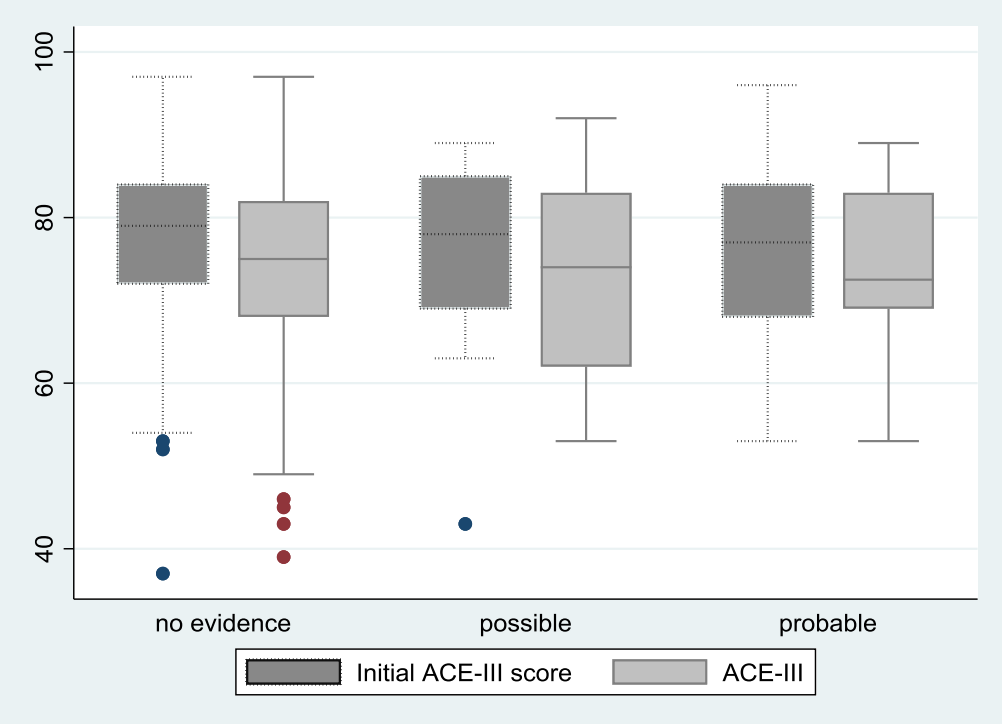

Figure 1. Change in ACE-III score by seizure category (boxplots indicate first quartile (Q1), median and third quartile (Q3) dots indicate outlier values (>1.5x interquartile range))

3.3.4 SEIZURE PREVALENCE

I determined a diagnosis of epilepsy in 37 (25.69%, 95% CI 19%-33%) patients (table 3.4) using the diagnostic criteria described above. 18 patients (12.50%) were categorised as 'Seizure Probable', 19 (13.19%) as 'Seizure Possible' and 107 (74.31%) as 'No Clinical Evidence of Epilepsy' (NCEE). The rate of 'Seizure Probable' participants is significantly higher than in the control population, in whom only one patient was found to have a remote history of epilepsy while none of the remaining 79 control patients were found to have any of the seizure features investigated in this study ($\chi^2(1, N=224)=8.347$ ($p=0.004$) . Illustrative cases from the PrESIDe study are described in appendix 5.

This suspicion of epilepsy had been documented in 10 patients prior to their assessment as part of the study. In the remaining 27 there was no previous evidence that epilepsy had been suspected.

This statistically significant difference in prevalence between groups was also seen upon restricting the group only to patients who received a diagnosis of Alzheimer's disease (102/144). Of these patients, 29/102 (28%) reported features suggestive of epilepsy, ($\chi^2(1, N=182)=23.45$ ($p<0.001$)).

There was a significantly higher rate of epilepsy in the MCI group than in the control group when combining probable and possible cases ($\chi^2(1, N=100)=4.17$ ($p=0.041$).

In patients with a primary diagnosis of vascular dementia 3/16 patients (18.75%) were included in the epilepsy probable group and 1/16 (6.25%) were included in the epilepsy possible group. This represented a significant increase compared to controls for the combined probable and possible patients ($\chi^2(1, N=96)=15.08$ ($p<0.001$).

3.3.5 SEIZURE FEATURES

The most common seizure type was impaired awareness / behavioural arrest seizures. This was seen in 15 of the Probable Epilepsy group (83%). 4 patients in this group (22%) experienced generalised tonic-clonic seizures. A range of further seizure features were also seen (table 3.4). These included motor automatisms, sensory abnormalities (including olfactory hallucinations), amnesia on waking, and focal onset motor seizures.

	ID	diagnosis	memory clinic ACE-III	PrESIDe ACE-III	Age of onset (memory)	memory onset to seizure onset	Seizure Features
Epilepsy Probable	EX084	AD	84	83	71	2 years	AW, MA, A, GTC
	EX138	AD	74	72	66	8 years before	AR, AW, MA, GTC
	EX001	AD	78	71	84	2 years	AR, AW, MA, A
	EX017	AD	60	62	81	2 years	AR, AW, MA, A
	EX054	AD	89	89	76	6 months	AW, MA, OH
	EX096	AD	60	53	70	18 months	AR, AW, MA
	EX134	AD	73	72	74	3 years	AR, AW, MA
	EX062	VASC	68	62	74	1 year	AR, AW, GTC
	EX026	LBD	53	68	71	since childhood	MA, A, GTC
	EX059	AD	67	73	83	1 year	AR, AW
	EX095	AD	72	85	72	18 months	AR, SA
	EX108	AD	79	86	72	6 months	AR, A
	EX145	AD	86	81	79	since childhood	AR, MA
	EX149	VASC	76	70	73	same time	AR, FOS
	EX131	MCI	96	89	79	2 years	AR, AW
	EX080	AD	84	83	72	6 months	AR
	EX139	AD	79	69	75	2 years	AR
	EX092	VASC	87	77	77	18 months	AR
Epilepsy Possible	EX015	LBD	89	56	72	4 years	AR, AW, MA
	EX048	AD	66	63	75	3 years	AR, AW, MA
	EX119	AD	84	82	75	3 years	AW, MA
	EX018	AD	43	56	66	18 months	AR, AW
	EX028	AD	75	77	89	1 year	AR, AW
	EX032	AD	63	62	89	2 years	AR, AW
	EX043	AD	83	77	75	18 months	AW, MA
	EX112	AD	73	84	51	5 years	AW, MA
	EX005	AD	79	83	81	18 months	AR
	EX027	AD	86	85	79	3 years	AR
	EX035	AD	22/30 (MMSE)	53	86	2 years	AW
	EX037	AD	67	66	83	6 months	AR
	EX065	AD	88	81	87	12 months	AR
	EX081	AD	78	74	65	2 years	AR
	EX083	AD	69	66	74	1 year	AW
	EX117	AD	70	60	80	1 year	AR
	EX136	AD	78	74	77	2 years	AR
	EX042	VASC	85	85	75	2 years	AR
	EX107	MCI	89	92	69	6 months	AR

key: **Diagnosis**: AD - probable Alzheimer's disease, VASC - vascular dementia, LBD - Lewy Body dementia, MCI - Mild Cognitive Impairment. **Seizure Features**: AR - altered responsiveness, AW - amnesia on waking, MA - motor automatisms, GTC - generalised tonic-clonic seizures, OH - olfactory hallucination, FOS - focal onset seizure, A - aura, SA - sensory abnormality

Table 3.4: characteristics of patients in epilepsy possible and probable groups

Combining the epilepsy possible and epilepsy probable groups, the mean reported duration from the onset of memory symptoms until the first seizure, based on informant accounts was 12.2 months (median 18 months, range -96 to 60, excluding two patients with onset of epilepsy in childhood) (Figure 3.2).

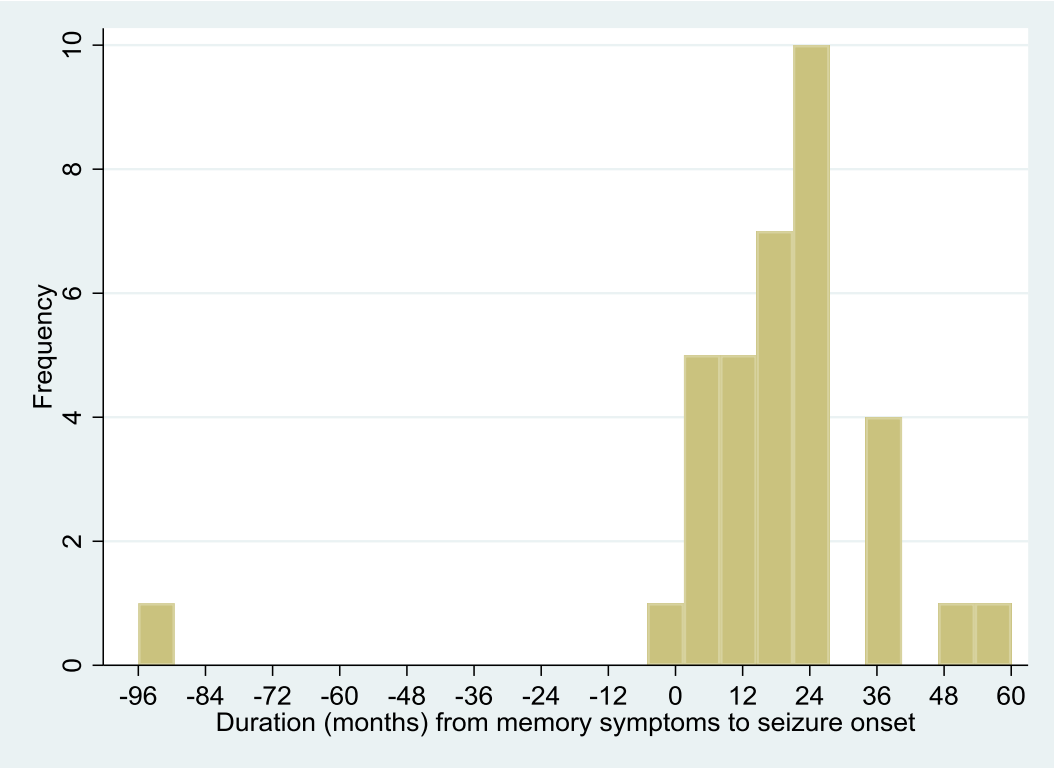

Figure 3.2: time from memory symptom onset to seizure onset in epilepsy possible and probable participants

The results of the informant completed questionnaires (CBI-R and CDR questionnaires) are shown in table 3.5, revealing a significant difference in both measures when the epilepsy probable group (and the combined probable and possible group) is compared with the NCEE group.

	CDR-SOB (mean, SD)	CDR-global score (mean, SD)	CBI-R (mean, SD)
PrESIDe total	3.96 (2.76)	0.74 (0.48)	40.40 (26.58)
No clinical evidence of Epilepsy	3.52 (2.47)	0.68 (0.45)	35.32 (24.40)
Epilepsy Possible	4.56 (2.65) p=0.130	0.81 (0.4) p =0.280	54.27 (24.5) p=0.006
Epilepsy Probable	6.19 (3.1) p<0.001	1.03 (0.65) p=0.007	54.29 (30.91) p=0.006
Combined possible and Probable	5.39 (3.0) p<0.001	0.92 (0.55) p=0.016	54.28 (27.64) p<0.001
(P-values for epilepsy groups vs no clinical evidence of epilepsy)			

Table 3.5: comparing informant questionnaires across seizure categories

3.3.6 MEDICATION

Of the 144 patients in our study 40 were taking a medication (Donepezil (29), Rivastigmine (7) or Memantine (4)) specifically licenced for the treatment of dementia in the UK. There was no significant difference in the prevalence of the use of these medications between the combined epilepsy group (11/37, 29.7%) and the NCEE group (29/107, 27.1%). Six patients in the epilepsy probable group were prescribed an anti-epileptic medication at the time of assessment (Lamotrigine (2), Levetiracetam (2), and Sodium Valproate (1), Phenobarbitone (1)). This group included the two patients with seizures since childhood, and one patient who had experienced seizure onset 8 years prior to the onset of memory symptoms. Of the remaining patients, 2 had experienced generalised tonic-clonic seizures and one had experienced focal onset seizures following a stroke. In addition, one patient in the NCEE group was currently prescribed Carbamazepine for the treatment of neuropathic pain. No other participants were on anti-epileptic medication for any other indication. Therefore 66.67% patients in the probable group and 100% in the possible epilepsy group were not on anti-epileptic treatment at the time of the study.

3.4 DISCUSSION

The prevalence of epilepsy is increased among patients with dementia but the extent of this increase remains controversial. I have identified a prevalence of clinically diagnosed epilepsy of between 12.5 and 25.7% in a memory clinic

population with MCI and early dementia, using a standardised proforma to elicit symptoms suggestive of epilepsy in interviews with patients and their carers. To our knowledge, this is the first UK based study that has recruited a population of participants from the memory clinic, with all dementia diagnoses, and aimed to investigate the prevalence of epilepsy in this group.

The seizures were predominantly subtle and non-convulsive, and started on average less than two years after memory symptom onset. While cognitive performance did not differ between patients with or without epilepsy, patients with epilepsy were more impaired on standard measures of behavioural performance assessed by informant interview. Given suggestive evidence (Belcastro et al., 2007, Vossel et al., 2013, Vossel et al., 2016) from other work that epilepsy can accelerate cognitive decline in patients with dementia, these results may challenge current practice which tends to overlook subtle seizures in patients with dementia and to be reluctant to treat epilepsy given the potential side-effects of anti-epileptic medication (Mendez and Lim, 2003, Larner, 2010, Liu et al., 2016). I consider each of these main findings in turn before considering limitations of our study.

3.4.1 PREVALENCE

The prevalence of epilepsy in our memory clinic sample was significantly increased when compared to a population without cognitive impairment matched for age, gender and education. This increase was seen for the memory clinic population as a whole, but also for patients with Alzheimer's disease, vascular dementia and MCI when these conditions were considered separately. Patients with seizures did not differ from those without epilepsy in age at dementia symptom onset, duration of symptoms or cognitive test score. Epileptic seizures were not a feature of advanced disease in these patients.

3.4.2 CLINICAL FEATURES

The seizures in our patients were often subtle and easily missed. Brief periods of unresponsiveness, behavioural arrest and staring were common. In many cases, these features had been noted previously, but had been considered a feature of the underlying dementia, rather than as evidence of epilepsy. The features described in our participants are in keeping with previous research in this area

which has shown that only a minority of patients experience generalised tonic-clonic seizures (Belcastro et al., 2007, Vossel et al., 2016, Horvath et al., 2018). Moreover, it is in keeping with the reported semiology of temporal lobe epilepsy, where more subtle features such as staring, blinking and behavioural arrest are frequently described, particularly in more elderly populations (Villanueva and Serratosa, 2005, Fogarasi et al., 2007, Blair, 2012). The spectrum of mesial temporal lobe epilepsy also includes transient epileptic amnesia (TEA), in which seizures are characterised by brief periods of amnesia during which other cognitive functions remain intact (Butler et al., 2007, Mosbah et al., 2014). It is possible that seizures of this nature also occur in patients with dementia, but would be particularly difficult to identify given the baseline cognitive deficits in these patients. However, the presence of olfactory hallucinations, and episodes of amnesia on waking in our group, which have frequently been described in patients with TEA (Atherton et al., 2014, Savage et al., 2017), suggests that seizures similar to those described in TEA can occur in patients with dementia, as previously reported (Krishnan and Larner, 2009, Cretin et al., 2014).

3.4.3 COGNITIVE DECLINE

The ACE-III examination scores for the group as a whole were significantly lower at the time of study assessment than at memory clinic baseline. In all three seizure sub-groups there was a drop in the ACE-III score between baseline memory clinic assessment and study assessment. This drop was largest in the epilepsy possible group, but only reached statistical significance in the large NCEE group, probably as a result of its size and the resulting statistical power to detect such a change. The differences between groups was not significant at either time point.

However, the CDR-SOB was significantly higher in the epilepsy group than in the NCEE group. This difference suggests that seizures in these patients are associated with accelerated impairment in terms of activities of daily living and an increased disease burden as identified by the people spending the most time with these patients – typically their spouse. This score, which reflects observations by carers over a number of weeks or months is likely to be more sensitive to global impairment than a single cognitive test result (O'Bryant et al., 2008, O'Bryant et al., 2010, Eldholm et al., 2018).

It is unclear from our data whether the seizures in our patients are a cause of more severe impairment – i.e. lead to accelerated decline – or reflect a more severe form of disease which independently causes accelerated functional impairment with epileptic seizures as an incidental feature, However, numerous studies, looking at mouse models of dementia have investigated this question (Palop et al., 2007, Gurevicius et al., 2013, Ovsepian and O'Leary, 2015). These studies report that the pathological changes seen in Alzheimer's disease are associated with neuronal hyperexcitability which increases the potential for epileptic seizures to occur (Palop et al., 2007, Brown et al., 2011, Stargardt et al., 2015, Booth et al., 2016). In addition further studies have shown that the epileptic seizures seen in these models facilitate the more rapid and anatomically diffuse spread of Alzheimer's pathology which has been associated with an accelerated cognitive decline in these animals (Palop and Mucke, 2009, Scharfman, 2012). Current trials investigating the effects of anti-epileptic medication in both human patients with dementia and epileptic seizures, and others studying animal models of these conditions, will shed further light on this issue (Bakker et al., 2015, Nygaard et al., 2015).

3.4.4 IMPLICATIONS

It is clear that patients and their carers are rarely aware themselves of the risk of epileptic seizures in dementia and have not been prepared to recognise them if they occur. Providing education about the risk of epilepsy for those caring for people with dementia would help to identify patients with seizures earlier in the clinical phase of their illness and therefore increase the window of opportunity to provide anti-epileptic treatment.

3.4.5 LIMITATIONS

I diagnosed probable and possible epilepsy in this study based on clinical grounds. Whilst the clinical history obtained in these patients is suggestive of epileptic seizures and in keeping with the seizure phenotypes described elsewhere (Vossel et al., 2013, Vossel et al., 2016) it would be beneficial to have confirmatory evidence, provided by EEG recordings, of the presence of abnormal epileptiform activity to support this diagnosis. However, as has been shown in previous work (Liedorp et al., 2010, Horvath et al., 2016), standard clinical EEG

is not a sensitive means of identifying abnormalities in these patients. Research has shown that more prolonged EEG recordings, especially those that involve overnight recordings and sample sleep, are particularly valuable in these patients (Horvath et al., 2017). In our study, participants were routinely asked if they had had an EEG performed, only two patients recalled this. In both cases the reports of these recordings were reviewed. In one case clear epileptiform abnormalities were identified (Left fronto-temporal (EX138)). In the other case no clear abnormalities were reported (EX149).

I diagnosed and subtyped dementia in this study on clinical grounds, supporting the diagnosis of MCI using standard neuropsychological testing. Whilst recent developments in the use of biomarkers have shown these to be useful in confirming diagnoses, clinical decision making based on the history provided and the findings on examination remains a sensitive means of reaching a diagnosis in these patients. This is the approach advocated by the diagnostic criteria for AD which emphasise that the core clinical criteria provide very good diagnostic accuracy and that whilst biomarker evidence 'may increase the certainty' that the diagnosis is due to AD pathology they are often uninformative when a diagnosis of probable AD is made (McKhann et al., 2011). The utility of these biomarkers increases when the diagnosis is less certain, in atypical cases of dementia, in the earlier stages of disease, or in predicting the likelihood of progression from MCI to dementia (Blennow et al., 2015, Olsson et al., 2016, Simonsen et al., 2017).

I report the prevalence of epileptic seizures in patients recruited from a regional memory clinic. Given that all patients in whom there is a suspicion of dementia should be referred to this service, our results should also reflect prevalence rates for patients with MCI or dementia in the community more widely. However, as this is not a true community-based study our findings should be extrapolated with caution. Likewise, whilst the memory clinic could be considered to represent patients who are early in the course of clinical disease, I have shown a wide variation in both the duration of memory symptoms prior to assessment in the memory clinic and the cognitive performance as measured by ACE-III testing at this time and therefore our group does not definitively represent the prevalence of epilepsy in patients with MCI or early dementia. I can, however, be confident that the patients recruited to this study are representative of the memory clinic population more broadly, in terms of age, gender and cognitive function.

As indicated above, our data cannot answer the question of whether dementia-related seizures accelerate cognitive or behavioural decline. There is suggestive evidence that this may be so (Vossel et al., 2016) and current trials will help to answer the question of whether anti-epileptic medication is beneficial (Bakker et al., 2015, Musaeus et al., 2017). At present many clinicians are reluctant to prescribe anti-epileptic medications in these patients due to concerns with their cognitive side effects, compliance, interaction with other medications and potential for commonly used medications to lead to problems with sleep. In our study the only patients currently prescribed anti-epileptic medication were those with seizure onset during childhood/adolescence, with a long interval (8 years) from the onset of seizures to the onset of memory symptoms, or who had had witnessed generalised tonic-clonic seizures, or focal onset seizures following a stroke.

3.5 CONCLUSION

The prevalence of epileptic seizures is increased in patients diagnosed with MCI or dementia. The onset of seizures in our patient group occurred within two years of the reported onset of memory symptoms. At the time of seizure onset, patients with seizures were not different to those without seizures in terms of age or cognitive test score, but were significantly more impaired on measures of the global impact of dementia.

Declaration:

This chapter has been published as: Baker, J., Libretto, T., Henley, W. & Zeman, A. (2019). The prevalence and clinical features of epileptic seizures in a memory clinic population. *Seizure,* 71**,** 83-92. This paper was written by me and reviewed prior to publication by TL, WH and AZ. The study design, data collection and analysis were all performed by me. TL provided contact details for control participants. WH provided support for statistical analysis

CHAPTER FOUR: THE PRESENTATION OF EPILEPTIC SEIZURES IN DEMENTIA: A 12-MONTH FOLLOW-UP STUDY

4.1 INTRODUCTION

The prevalence of epileptic seizures is increased in patients in the early clinical stages of dementia when compared to an age-matched cognitively normal population (Cheng et al., 2015, Cook et al., 2015, Nicastro et al., 2016). In The Presentation of Epileptic Seizures in Dementia (PrESIDe) study I identified a prevalence of epilepsy between 12.5 and 25.7 percent in these patients (Baker et al., 2019). These findings are comparable to those of recent studies in this field (Vossel et al., 2013, Vossel et al., 2016, Horvath et al., 2017, Horvath et al., 2018). However, the long-term sequelae of epilepsy in this population remain unclear. Does the presence of epileptic seizures impact the progression of dementia and what is the nature and extent of this effect?

The aim of this study is to answer these questions through a 12-month follow-up assessment of patients initially recruited to the PrESIDe study. Our goal is to ascertain the rate of cognitive decline in patients in whom a suspicion of epilepsy has been identified and to compare this with those in whom there was no suspicion of epilepsy. The initial findings of the PrESIDe study did not identify a significant difference in cognitive performance between these groups at the time of their initial memory clinic assessment or at the time of their recruitment in to the study. However, there was a difference in scores on informant completed questionnaires (Cambridge Behavioural Inventory - Revised and Clinical Dementia Rating (CBI-R and CDR)) which suggested increased difficulty in completing activities of daily living (ADLs) and greater care requirements in patients with dementia who also experienced epileptic seizures.

4.2 MATERIALS AND METHODS

I recruited patients to the PrESIDe study as outlined previously in chapter 3. 11 months after their initial study assessment, participants were contacted via a letter to remind them of the study and to outline a plan to review them again. Letters were followed by a telephone call to schedule a follow-up visit. These interviews were to be performed 12 months (+/- 2 weeks) after their initial visit,

where possible in the same location, at the same time of day and in the presence of the same informant who was in attendance for the initial interview. To minimise sampling bias contact details were stored on a separate spreadsheet to diagnosis and previous suspicion of epilepsy and the telephone contact protocol (a three-strike system) was employed for all participants).

Assessments consisted of a brief interview to identify whether any further episodes suggestive of epilepsy had occurred, or if none had been identified at the time of the first interview, whether this had changed; as well as brief questioning to update information on medical history (any changes to medication, recent illnesses / surgery etc.) over the intervening 12-months. Subsequently, cognitive testing was repeated using the Addenbrooke's Cognitive Examination - Version III (ACE-III). At the same time, the informant was asked to complete the same two questionnaires (CDR and CBI-R) in order to compare these with those previously completed.

Between-group analysis of demographic features, cognitive test performance and informant completed questionnaire scores was performed using independent sample t-tests and chi-square testing. Multiple linear regression analysis was performed to assess the relationship between dependent and independent variables. Statistical significance was judged as any p-value <0.05. IBM SPSS statistics 22.0 and STATA were used to perform data analysis.

Ethical approval for this project was awarded through the Integrated Research Application System (IRAS) and provided by the London – Bromley Research Ethics Committee.

4.3 RESULTS

4.3.1 PATIENT DEMOGRAPHIC FEATURES

144 patients were assessed and included in the initial study. Between the initial visit and the 11-month mail-out 8 patients had died (Figure 4.1). From this remaining sample of 136, the research team was unable to contact 22 patients and 12 patients declined further assessment. This resulted in a total of 102 participants receiving a 12-month follow-up assessment.

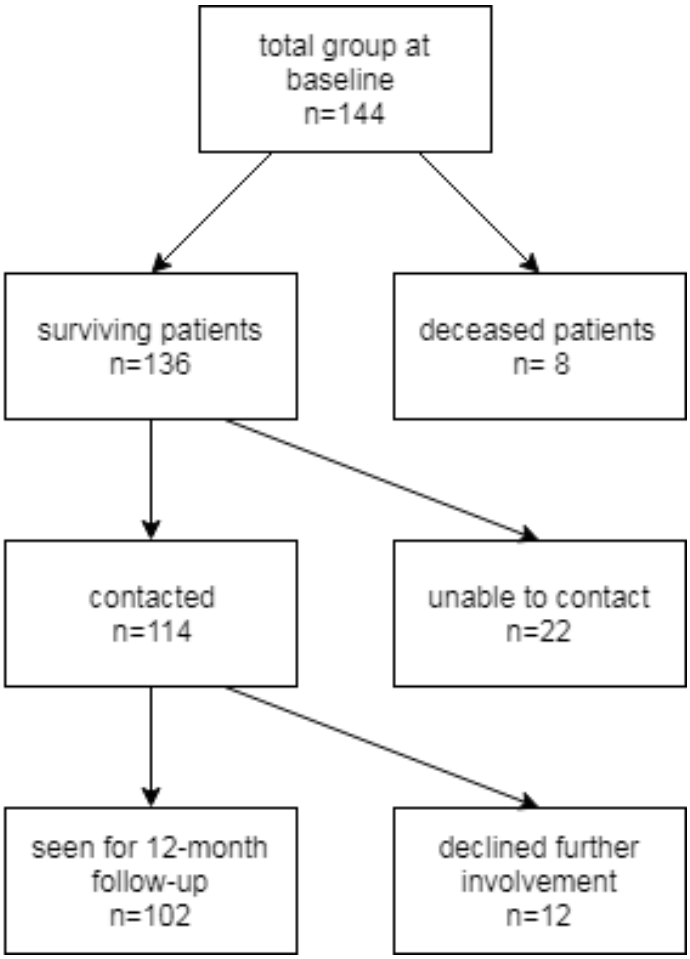

Figure 4.1: flow-diagram showing size of PrESIDe cohort

The demographic features of the group (n=102) are summarised in Table 4.1 alongside the features of the total group seen at initial assessment (n=144) for comparison. The participants seen for follow-up assessment did not differ significantly from the total group seen at baseline in terms of age, gender or ACE-III score at initial interview.

	Initial PrESIDe group (N=144)	12-month follow-up group (N=102)	
Age at baseline (mean, SD)	77.98, 6.75	77.79, 6.97	P=0.83
Gender (M:F)	76:68	56:46	P=0.743
ACE-III (at memory clinic)	76.25, 11.2	78.7, 10.2	P=0.081
ACE-III (at baseline visit)	74.17, 11.94	76.5, 11.1	P=0.122
Dementia Diagnosis:			
Alzheimer's Disease	102 (70.8%)	71 (69.6%)	P=0.84
Mild Cognitive Impairment	20 (13.9%)	16 (15.7%)	P=0.695
Vascular Dementia	16 (11.1%)	11 (10.8%)	P=0.94
Dementia with Lewy Bodies	4 (2.8%)	2 (2%)	P=0.691
Frontotemporal Dementia	1 (0.7%)	1 (1%)	P=0.798
Posterior Cortical Atrophy	1 (0.7%)	1 (1%)	P=0.798
Seizure Diagnosis:			
Probable (E-Pr)	18 (12.5%)	17 (16.7%)	P=0.354
Possible (E-Po)	19 (13.2%)	16 (15.7%)	P=0.581
No clinical Evidence of Epilepsy (NCEE)	107 (74.3%)	69 (67.6%)	P=0.252

(Table 4.1: comparing baseline characteristics of total PrESIDe group with group seen for 12-month follow-up)

4.3.2 COGNITIVE TEST SCORES

The differences between the no clinical evidence of epilepsy (NCEE) and the epilepsy groups (probable and possible, both combined and individually) were not significant at either the memory clinic or study baseline time points (Table 4.2). However, at the 12-month follow-up appointment the NCEE group had a significantly higher ACE-III test score than the epilepsy possible (E-Po) group (p=0.023) and the combined epilepsy (comb) group (p=0.007). There was a trend towards a similar difference between the NCEE group and the epilepsy probable (E-Pr) group at this time point (p=0.055).

	Memory clinic	PrESIDE baseline	PrESIDE 12-month	change baseline to 12/12
Total (n=102)	78.71 (10.12)	76.5 (11.14)	72.45 (13.62)	-4.05 (5.60)
NCEE (n=69)	79.84 (10.07)	77.36 (11.46)	74.93 (12.94)	-2.43 (4.3)
E-Po (n=16)	76.6 (8.45)	73.88 (11.09)	**66.31 (15.53)**	**-7.56 (7.27)**
E-Pr (n=17)	76.29 (11.43)	75.47 (9.93)	68.18 (12.20)	**-7.29 (5.92)**
Comb (n=33)	76.44 (9.98)	74.70 (10.37)	**67.27 (13.72)**	**-7.42 (6.5)**

Table 4.2: ACE-III test scores at different time points, with subjects categorised by suspicion of epilepsy, figures in bold indicate significant difference ($p<0.05$) when compared to NCEE group)

The decline in ACE-III scores between the baseline and 12-month follow-up assessment was significantly larger when comparing both the E-Po ($p<0.001$), E-Pr ($p<0.001$) and Comb ($p<0.001$) groups to the NCEE group (Figure 4.2). There was no significant difference between the E-Po and E-Pr groups at any time point in this measure. Whilst all groups showed a decline in ACE-III scores between baseline and 12-month assessments this difference was only significant in the combined group ($p=0.016$).

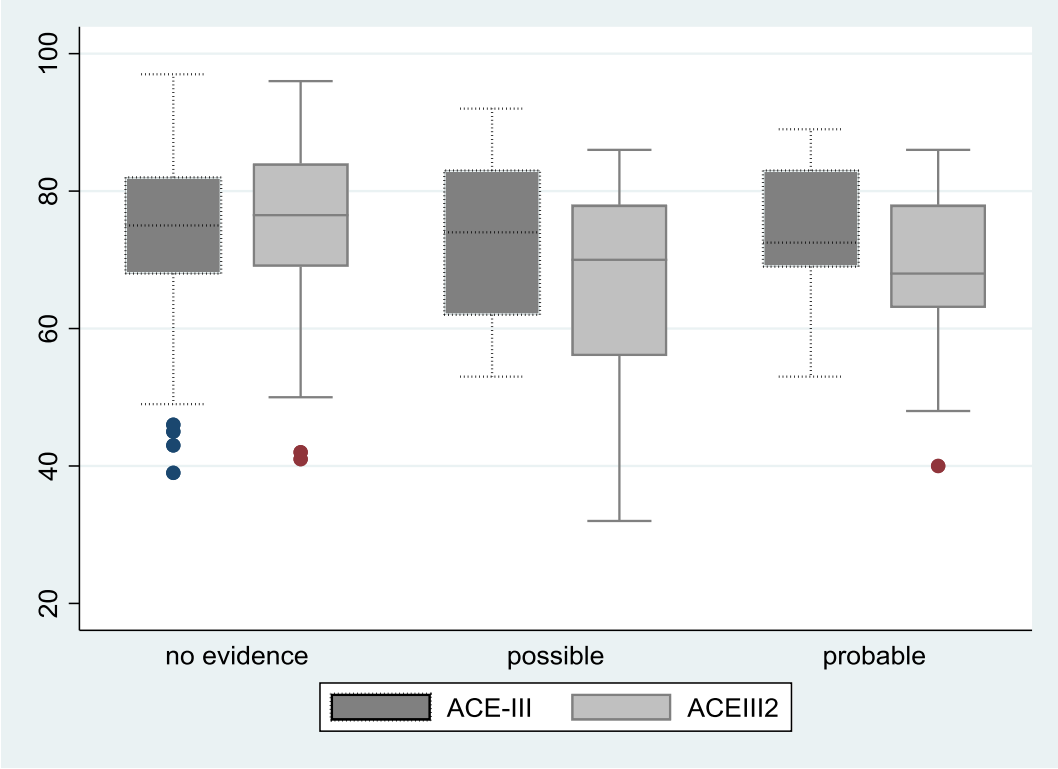

Figure 4.2: change in ACE-III scores between baseline and 12-month PrESIDe assessments

With the exception of the language domain in the NCEE group, all groups demonstrated a decrease in score in all domains at 12-month follow-up when compared to their baseline assessment (Table 4.3). Patients in whom epilepsy was suspected (probable, possible and combined groups) experienced a greater decrease in test scores in all cognitive domains tested by the ACE-III. The size of this difference was greatest in the attention and fluency domains.

	Att	Att (2)	+/-	Mem	Mem (2)	+/-	Flu	Flu (2)	+/-
Total	82.3	76.6	-5.7	65.4	59.4	-6	56.7	50.6	-6.1
NCEE	82.9	79.9	-3	65.1	60.5	-4.6	58.6	54.6	-4
E-Po	78.8	**69.8**	-9	66.3	55.8	-10.6	48.2	**41.1**	-7.1
E-Pr	83.3	**69.9**	-13.4	65.6	58.4	-7.2	57.1	43.7	-13.4
Comb	81.1	**69.9**	-11.3	66.0	57.1	-8.9	52.8	**42.4**	-10.4
	Lang	**Lang (2)**	**+/-**	**Vis**	**Vis (2)**	**+/-**			
Total	87.6	86.8	-0.8	86.7	84.1	-2.6			
NCEE	89.0	89.4	0.4	87.9	86.2	-1.6			
E-Po	85.1	**81.3**	-3.8	84.8	77.3	-7.4			
E-Pr	84.6	**81.4**	-3.2	83.8	82.0	-1.8			
Comb	84.8	**81.4**	-3.5	84.3	79.7	-4.5			

Table 4.3: ACE-III domain scores at PrESIDe baseline and 12-month follow-up (bold figures indicate significant difference ($p<0.05$) when compared to NCEE group)

At the 12-month follow-up interview significant differences between the NCEE and Comb groups were present in the attention domain ($p=0.010$), fluency domain ($p=0.007$) and language domains ($p=0.004$) (Figure 4.3). The largest mean decline in raw score in the memory domain was seen in the E-Po patients (-10.6 points). However, there was no significant difference between groups in this domain (it was the largest decline in the NCEE group).

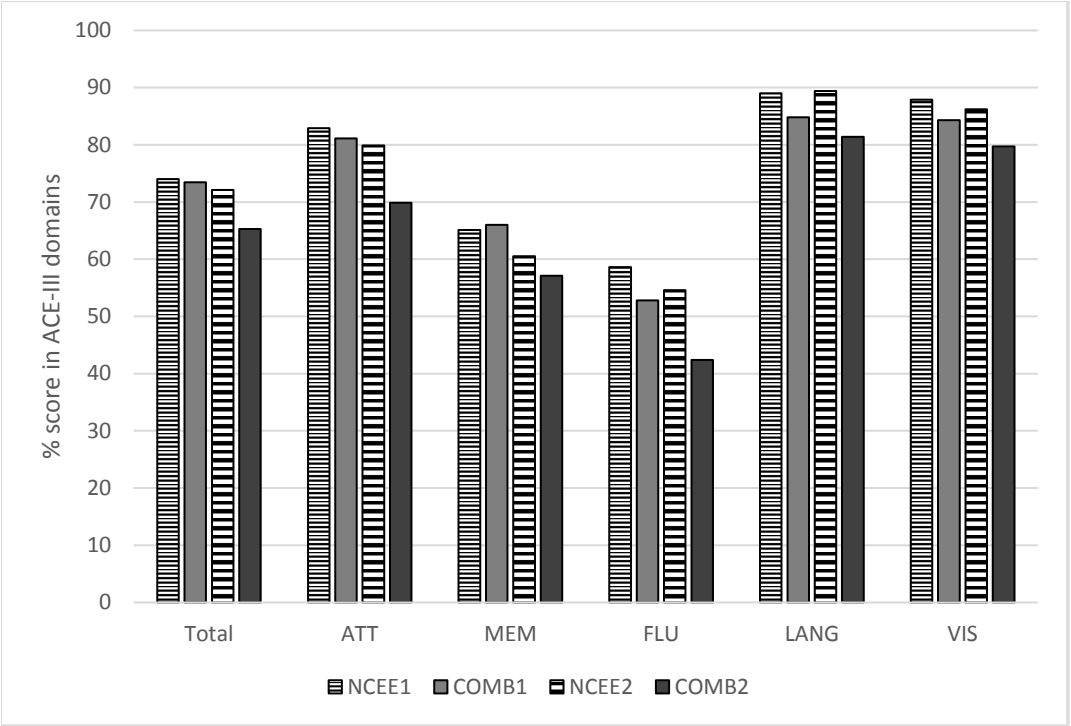

Figure 4.3. ACE-III total score and sub-domain scores (NCEE vs COMB)

4.3.3 INFORMANT COMPLETED QUESTIONNAIRES

All groups demonstrated an increase in CDR-SOB scores between baseline and 12-month interviews (Table 4.4). The increase in CDR was greatest in the NCEE group, although there was no significant differences between groups in this measure. Whilst the size of the increase in the CDR-SOB score was greatest in the NCEE group, the overall score was higher at both the baseline and 12-month follow-up interviews in the E-Pr, E-Po and Comb groups. This difference was significant between the NCEE and the E-Pr and Comb groups at both the baseline ($p<0.001$ (E-Pr), $p=0.004$ (Comb)) and 12-month interview ($p=0.007$ (E-Pr), $p=0.020$ (Comb)).

	CDR baseline	CDR 12-month	Change	CBI-R baseline	CBI-R 12-month	Change
Total	4.01 (2.79)	4.99 (3.55)	+0.98	39.91 (25.01)	50.94 (31.29)	+11.03
NCEE	3.37 (2.4)	4.38 (3.29)	+1.01	34.05 (21.61)	42.66 (28.13)	+8.61
E-Po	4.38 (2.79)	5.35 (4.05)	+0.97	**54.92 (24.42)**	**69.92 (33.32)**	+15
E-Pr	**6.13 (3.21)**	**6.97 (3.55)**	+0.84	**51.33 (30.43)**	**66.06 (30.07)**	+14.73
Comb	**5.34 (3.1)**	**6.24 (3.8)**	+0.9	**52.93 (27.47)**	**67.79 (31.05)**	+14.86

Table 4.4: Changes in CDR and CBI-R scores between baseline interview and 12-month follow-up bold figures indicate significant difference (p<0.05) when compared to NCEE group

	Mem1	Mem2	Change	Skill1	Skill2	Change	Care1	Care2	Change
NCEE	12.87	15.69	+2.82	4.13	5.69	+1.56	0.60	1.32	+0.72
E-Po	14.70	19.69	+4.99	**8.17**	**9.38**	+1.21	**2.58**	**3.15**	+0.57
E-Pr	**17.13**	**20.94**	+3.81	**7.20**	8.13	+0.93	**2.07**	2.75	+0.68
Comb	**16.04**	**20.38**	+4.34	**7.63**	**8.69**	+1.06	**2.30**	**2.93**	+0.63
	Behav1	**Behav2**	**Change**	**Mood1**	**Mood2**	**Change**	**Belief1**	**Belief2**	**Change**
NCEE	2.17	3.08	+0.91	2.40	2.86	+0.46	0.20	0.61	+0.41
E-Po	**6.00**	**5.54**	-0.46	**4.75**	4.08	-0.67	**0.92**	**2.38**	+1.46
E-Pr	3.67	4.94	+1.27	**4.13**	4.13	0.00	0.47	0.94	+0.47
Comb	**4.70**	**5.21**	+0.51	**4.41**	4.10	-0.31	**0.67**	**1.59**	+0.92
	Eating1	**Eating2**	**Change**	**Sleep1**	**Sleep2**	**Change**	**Motor1**	**Motor2**	**Change**
NCEE	1.65	1.90	+0.25	2.38	2.54	+0.16	3.10	3.34	+0.24
E-Po	1.67	3.46	+1.79	3.50	**5.15**	+1.65	4.67	**6.00**	+1.33
E-Pr	3.07	**5.00**	+1.93	3.53	**4.50**	+0.97	4.27	5.19	+0.92
Comb	2.44	**4.31**	+1.87	**3.52**	**4.79**	+1.27	4.44	**5.55**	+1.11
	Motiv1	**Motiv2**	**Change**						
NCEE	4.55	5.61	+1.06						
E-Po	**8.00**	8.85	+0.85						
E-Pr	5.80	**9.56**	+3.76						
Comb	6.78	**9.17**	+2.39						

Table 4.5: mean changes in CBI-R domain scores between baseline and follow-up assessments, bold figures indicate significant difference (p<0.05) when compared to NCEE group

All groups saw a significant increase between interviews in their CBI-R scores (Table 4.5). The largest increase was seen in the E-Po group. The increase in this group, as well as that of the E-Pr group was significant when compared to the NCEE group. On a domain-specific level the size of the mean increase in the epilepsy groups was greater than the NCEE group in the memory, belief, eating, sleep, motor domains and in addition in the E-Pr (but not E-Po) group in the motivation, and behaviour domains. Moreover, whilst the size of the change was greater in the NCEE group in the skill, care and mood domains - the overall scores at both the baseline and 12-month interviews remained greater in these domains in the E-Po ($p=0.003$), E-Pr ($p=0.005$) and combined groups ($p<0.001$).

4.3.4 FURTHER SEIZURES

8 patients reported having further witnessed seizure events between their initial study visit and their 12-month follow-up visit. In 3 cases this occurred in patients who had previously been classified as E-Po leading to their reclassification as E-Pr. For the purpose of their analysis in this chapter they have been included in their original group. The descriptions of these events are in keeping with those described in the previous chapter. No further generalised onset tonic-clonic seizures were reported. Most commonly seizures were focal non-motor onset events involving behavioural arrest, cognitive or sensory features. 3/8 patients who experienced further seizures were described as having motor automatisms at onset.

4.3.5 DECLINE IN PATIENTS ON ANTI-EPILEPTIC VS NOT ON ANTI-EPILEPTIC MEDICATION

6 patients had been taking an anti-epileptic medication between the time of their baseline and 12-month assessments. In these patients there was a smaller mean decline in ACE-III scores (-5.17) than in those not taking anti-epileptic medication (-7.93), which was not significant ($p=0.356$).

4.3.6 OTHER MARKERS OF COGNITIVE DECLINE

Of the 144 patients seen as part of the initial assessment, 6 had moved from their own home to a care setting (nursing home, residential home) by the time of the 12-month follow-up assessments. This included 4 (3.7%) in the NCEE group, and

2 in the epilepsy groups (1 E-Po (5.3%), 1 E-Pr (5.6%)). Over the same period 8 participant deaths occurred (6 in NCEE (5.6%), 2 in epilepsy group (5.4%)). These measures did not differ significantly between groups.

4.3.7 CHANGES IN DIAGNOSTIC CLASSIFICATION

There were no instances where a dementia diagnosis made at the time of initial assessment was changed at follow-up assessment. 4/16 (25%) patients diagnosed with MCI at initial assessment described a decline in function at their 12-month follow-up assessment which was significant enough to lead to a study diagnosis of dementia (AD in all cases) as outlined by validated diagnostic criteria (McKhann et al., 2011).

4.3.8 DIAGNOSTIC SPECIFIC CHANGES IN COGNITIVE TEST SCORES

A decline in cognitive scores was seen in all diagnostic groups. This change was greatest in the AD group (mean change -4.26, SD 5.81) and least in the MCI group (mean change -2.56, SD 4.5). Further analysis of the AD specific group is described below.

4.3.9 RESULTS IN PATIENTS WITH AD

72 (70.6%) patients seen at 12-months were diagnosed with Alzheimer's disease. The relative size of this group facilitated an independent subgroup analysis of the effects of seizures in patients with AD. Comparisons of the ACE-III, CDR and CBI-R scores in these patients are shown in tables 4.6-4.9 and figure 4.4.

	Memory clinic	PrESIDE baseline	PrESIDE 12-month	change baseline to 12/12
Total (n=72)	76.79 (9.25)	73.82 (9.92)	69.56 (12.79)	4.26 (5.81)
NCEE (n=45)	77.6 (9.7)	74.02 (9.83)	72.11 (11.51)	1.91 (3.69)
E-Po (n=14)	75 (7.86)	71.79 (10.12)	**63.71 (14.82)**	**8.07 (7.62)**
E-Pr (n=13)	75.77 (9.31)	75.31 (10.44)	67 (13.14)	**8.31 (5.62)**
Comb (n=27)	75.38 (8.45)	73.48 (9.31)	**65.3 (13.87)**	**8.19 (6.6)**

Table 4.6: ACE-III test scores in participants with AD at different time points, with subjects categorised by suspicion of epilepsy, figures in bold indicate significant difference ($p<0.05$) when compared to NCEE group)

At the 12-month follow-up interview the ACE-III score in the combined E-Po and E-Pr group was significantly lower than in the NCEE group (p=0.028). The ACE-III score in the E-Po group was also significantly lower than the NCEE group at the 12-month follow-up (p=0.030), whereas the E-Pr group was not significantly different to the NCEE group (p=0.177). The E-Po, E-Pr and comb groups showed a decline in all domains of the ACE-III test, with the largest declines seen in the attention, and fluency domains. The decline in all domains in this group was larger than those of the NCEE group. This supports the view that patients with Alzheimer's disease who experience epileptic seizures demonstrate a larger, multi-domain, decline in cognitive function than those without seizures. This is in contrast to the NCEE group, in whom the largest decline was seen in the memory domain, with relative stability in the language and visuospatial domains, and smaller declines in the fluency and attention domains.

	Att	Att (2)	+/-	Mem	Mem (2)	+/-	Flu	Flu (2)	+/-
Total	79.6	72.8	-6.8	60.5	54.4	-6	53.1	47.6	-5.5
NCEE	79.7	75.9	-3.8	58.9	54.5	-4.5	53.7	52	-1.8
E-Po	76.6	67.1	-9.5	63.5	53.3	-10.2	44.4	**36.7**	-7.7
E-Pr	82.5	68.4	-14.1	62.4	55.6	-6.8	60.4	44.5	-15.9
Comb	79.4	67.7	-11.7	63	54.4	-8.5	52.1	**40.5**	-11.6
	Lang	**Lang (2)**	**+/-**	**Vis**	**Vis (2)**	**+/-**			
Total	86.7	85.2	-1.5	85.6	83.4	-2.2			
NCEE	87.6	87.9	0.3	86.8	87.2	0.4			
E-Po	84.3	**79.7**	-4.7	83.5	**74.6**	-8.9			
E-Pr	86.1	81.7	-4.4	83.7	79.8	-3.8			
Comb	85.2	**80.6**	-4.6	83.6	**77.1**	-6.5			

Table 4.7: ACE-III domain scores in AD participants at PrESIDe baseline and 12-month follow-up, figures in bold indicate significant difference ($p<0.05$) when compared to NCEE group

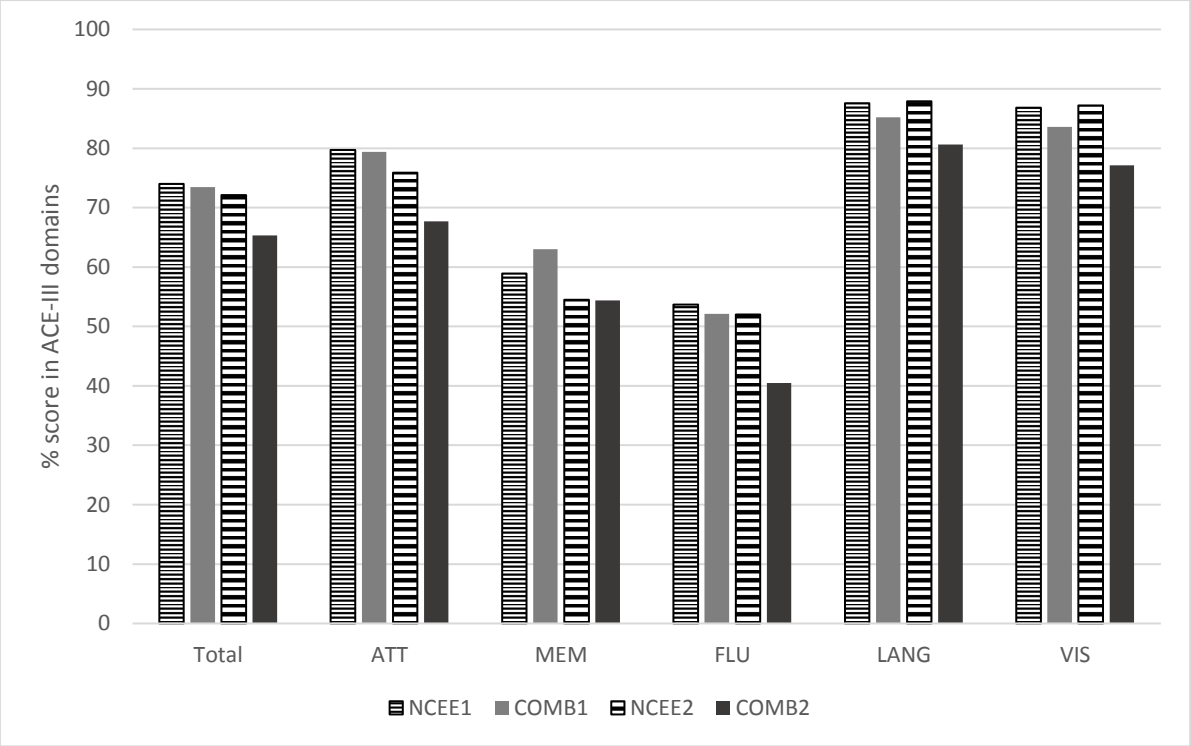

Figure 4.4. ACE-III total score and sub-domain scores (NCEE vs COMB, AD patients only)

	CDR baseline	CDR 12-month	Change	CBI-R baseline	CBI-R 12-month	Change
Total	4.2 (2.69)	5.2 (3.53)	+1	38.77 (22.68)	49.16 (25.26)	+10.39
NCEE	3.62 (2.46)	4.55 (3.26)	+0.93	32.69 (20.47)	40.03 (23.78)	+7.34
E-Po	4.67 (2.71)	5.67 (4.05)	+1	**55 (25.61)**	**72 (28.0)**	+17
E-Pr	**5.58 (2.98)**	**6.79 (3.52)**	+1.21	43.67 (19.74)	**57.92 (23.52)**	+14.25
Comb	**5.13 (2.83)**	**6.23 (3.76)**	+1.1	**49.09 (22.95)**	**64.65 (26.17)**	+15.56

Table 4.8: Changes in CDR and CBI-R scores in AD participants between baseline interview and 12-month follow-up figures in bold indicate significant difference ($p<0.05$) when compared to NCEE group)

Informant completed questionnaires highlighted significant differences between the epilepsy and non-epilepsy groups at both time points. However, when the analysis was limited to patients with AD, there was no significant difference between the NCEE and E-Pr groups on the CBI-R at baseline ($p=0.092$). The CBI-R scores were significantly greater for the E-Po, E-Pr and combined groups at the 12-month interval ($p<0.001$ (E-Po), $p=0.02$ (E-Pr), $p<0.001$ (comb)). As had

been the case for the total PrESIDe cohort the CDR-SOB was significantly greater in the E-Pr (p= 0.019) and combined groups (p=0.020) at the time of their baseline assessments and also at the time of the follow-up assessments (p=0.036 (E-Pr), p=0.05 (comb). On this measure there was no significant difference between the NCEE and the E-Po group at either time point (p= 0.179 (baseline), p= 0.294 (12-month)).

	Mem1	**Mem2**	**Change**	**Skill1**	**Skill2**	**Change**	**Care1**	**Care2**	**Change**
NCEE	13.3	15.6	+2.3	3.8	5.3	+1.5	0.2	0.8	+0.6
E-Po	14.9	**21**	+6.1	**8.1**	**10.2**	+2.1	**2.8**	**3.5**	+0.7
E-Pr	16.3	**19.7**	+3.4	6.4	7.1	+0.8	**1.5**	**2.3**	+0.8
Comb	15.6	**20.3**	+4.7	**7.2**	**8.6**	+1.4	**2.1**	**2.9**	+0.8
	Behav1	**Behav2**	**Change**	**Mood1**	**Mood2**	**Change**	**Belief1**	**Belief2**	**Change**
NCEE	1.8	2.8	+1	2.3	2.6	+0.3	0.1	0.5	+0.4
E-Po	**5.6**	**5.6**	0	**4.9**	3.9	-1	**0.9**	**2.7**	+1.8
E-Pr	2.5	3.6	+1.1	**3.8**	3.7	-0.1	**0.6**	1	+0.4
Comb	**4**	**4.6**	+0.6	**4.3**	3.8	-0.5	**0.7**	**1.8**	+1.1
	Eating1	**Eating2**	**Change**	**Sleep1**	**Sleep2**	**Change**	**Motor1**	**Motor2**	**Change**
NCEE	1.5	1.6	+0.1	2.3	2.5	+0.2	3.4	3	-0.4
E-Po	1.7	**3.8**	+2.1	3.5	**5.4**	+1.9	4.4	**6**	+1.6
E-Pr	1.9	**4.2**	+2.3	3	**4.1**	+1.1	3.5	4.3	+0.8
Comb	1.8	**4**	+2.2	3.3	**4.7**	+1.4	3.9	**5.1**	+1.2
	Motiv1	**Motiv2**	**Change**						
NCEE	3.9	5.2	+1.3						
E-Po	**8.1**	**9.8**	+1.7						
E-Pr	4.3	8.2	+3.9						
Comb	6.1	**9**	+2.9						

Table 4.9: mean changes in CBI-R domain scores in AD participants between baseline and follow-up assessments (higher scores indicate greater impairment, figures in bold indicate significant difference (p<0.05) when compared to NCEE group)

On the CDR, the greatest differences between the combined E-Pr and E-Po group and the NCEE group were in the judgement and problem solving domain (0.56 points) and the personal care domain (0.47 points). The smallest differences were in the memory (0.1 points) and the orientation (0.11 points)

sections. In contrast, for the CBI-R the most instructive questions (difference >1.0) were found to be Memory 5 (Forgets the names of objects and things), Memory 8 (Becomes confused or muddled in unusual surroundings), and Sleep 2 (Sleeps more by day than before). Sleep 2 demonstrated the largest difference between these groups using the CBI-R (1.6 points).

4.3.10 DECLINE RELATED TO USE OF DEMENTIA MEDICATION

25/72 patients diagnosed with AD in our cohort (34.7%), were taking a medication prescribed for the treatment of their dementia between their baseline and 12-month assessments (18 Donepezil, 5 Rivastigmine, 2 Memantine). Whilst both groups saw a decrease in their ACE-III scores, this decrease was greater in the patients taking medication than in those that were not (-5.36 (SD 6.74) vs. -3.68 (SD 5.24)). However, this difference was not significant (p=0.246).

4.4 DISCUSSION (WHOLE COHORT)

Patients with dementia who experience epileptic seizures exhibit an accelerated decline in cognitive function when compared to patients with dementia in whom there is no clinical suspicion of epilepsy. This is demonstrated by a fall in the mean ACE-III score from 77.36 to 74.93 (2.43 points) in the NCEE group and from 74.7 to 67.27 (7.42 points) in the combined epilepsy groups. Whilst the NCEE group had a higher ACE-III score at the time of their initial memory clinic appointment and their baseline PrESIDe assessment, the difference in scores between this group and the combined epilepsy group only became significant at the time of the 12-month follow-up assessments. This difference was even greater when the study population was restricted only to patients with Alzheimer's disease. In this analysis the decline in ACE-III scores was 1.91 in the NCEE group and 8.19 in the combined group ($p < 0.001$).

Through a domain specific analysis of the ACE-III scores I have shown that a decrease in performance occurs in all domains. The largest decreases in the epilepsy groups were seen in the attention, fluency and memory components of the test. The difference in the decline between the epilepsy and non-epilepsy groups was greatest in the attention and fluency elements of the test. Whilst all patients with dementia exhibit a decrease in cognitive function over time, those

with epilepsy decline in a manner which is both greater and involves more domains, leading to the significant difference across the ACE-III total score.

The main question raised by these results is whether epilepsy is a marker for a more severe form of disease in these patients, or whether epilepsy is a driver of these more rapid changes. The progression of clinical symptoms in AD is associated with the spread of the amyloid-β (Aβ) plaques and phosphorylated tau (p-tau) neurofibrillary tangles into different regions of the brain (Braak and Braak, 1995, Braak and Del Tredici, 2015). In AD patients who experience epileptic seizures a more rapid decline occurs across all domains. The reasons for this are not clear, although several studies have investigated the association between neuronal hyperexcitability and the spread of tau (Lewis and Dickson, 2016, Passamonti et al., 2018, Kaufman et al., 2018), suggesting that seizures can contribute to the spread of tau through both trans-neuronal (Su et al., 1997, Cope et al., 2018, Kim et al., 2018) and trans-synaptic (Liu et al., 2012, Dujardin et al., 2014, Wang et al., 2017) means. Additionally, studies utilizing tau-PET have shown a direct correlation between the distribution of tau and cognitive impairment in patients with dementia (Ossenkoppele et al., 2016, Hanseeuw et al., 2019). It is possible that in patients with epileptic seizures the more rapid decline in cognitive function is related to an accelerated propagation of tau as a result of their epileptic seizures (Pooler et al., 2013, Tai et al., 2016). Conversely, it is also possible that some patients with AD experience a more aggressive form of this disease and that this phenotypic heterogeneity also gives rise to epileptic seizures in these patients.

4.4.1 FASTEST AND SLOWEST DECLINE

Of the 10 patients with the largest fall in ACE-III scores between baseline study visit and 12-month follow-up (fall of at least 11 points), 7 of these were categorised as having possible or probable epilepsy (2 E-Po, 5 E-Pr). Of these 7 patients, only 1 was taking anti-epileptic medication (Levetiracetam). However, not all 10 of these fastest decliners showed evidence of epilepsy; other factors may also contribute to the rate of cognitive decline in these patients. These factors have previously been investigated and include age (at onset of memory symptoms and overall chronological age), duration of memory symptoms, family history of dementia and medical comorbidities (Bowler et al., 1998, Suh et al.,

2004, Musicco et al., 2009, Roselli et al., 2009). Conversely, of the 10 patients with the smallest decline in ACE-III scores, 2 of these were in the epilepsy groups (1 E-Po, 1 E-Pr). Of the 2 patients with a suspicion of epilepsy in this group, 1 of them was on anti-epileptic medication (Sodium Valproate and Lamotrigine).

4.4.2 ANTIEPILEPTIC MEDICATION

I did not identify a significant difference in cognitive decline between patients treated with antiepileptic medications and those that were not. It is possible that the lack of a significant difference is a result of the small size of these groups, or the limited duration of follow-up obtained. Other studies looking at the role of anti-epileptic medication in patients with dementia and animal models of dementia have reported conflicting outcomes (Belcastro et al., 2007, Cumbo and Ligori, 2010, Sanchez et al., 2012, Nygaard et al., 2015). These may be explained by differences in patient selection, duration of therapy or drug dosage. Improving our understanding of the timing and semiology of seizures in patients with dementia may lead to the better identification of patients who would be most likely to benefit from the initiation of anti-epileptic medication.

Informal discussion with the clinicians referring into our study indicated hesitation about the use of anti-epileptic medications in patients with MCI and dementia, a view supported by the small number of patients who received treatment for their epilepsy in our cohort. This partly reflected concern about the possible cognitive side effects of these medications (Ortinski and Meador, 2004, Cumbo and Ligori, 2010, Eddy et al., 2011). It is therefore reassuring to know that the use of anti-epileptic medications was not associated with faster cognitive decline in our cohort. However, our study was not designed to interrogate the cognitive effects of anti-epileptic medication in these patients and further work is required to investigate the potential risk and benefits of the wider use of these medications in patients with dementia. Multiple trials are currently underway on this topic (Vossel, 2019).

4.4.3 ACETYLCHOLINESTERASE INHIBITORS

No significant difference was identified in the cognitive decline in patients with AD taking acetylcholinesterase inhibitors, or other medications licensed for the treatment of AD, versus those that were not. In our cohort there was a difference

between the ACE-III scores at baseline between these two groups that may explain this difference (70.75 in treated group vs 75.35 in untreated group), although this difference was not significant (p=0.063). There is however extensive evidence of the beneficial role of acetylcholinesterase inhibitors in Alzheimer's disease (Howard et al., 2012, Lee et al., 2015). Our study was not designed to investigate the role of these medications and no effort was made to match those on these medications with those that were not at the time of their baseline assessment.

4.4.4 MCI CONVERSION

In our study, 25% of patients initially diagnosed with MCI at their initial assessment subsequently had this diagnosis changed to AD at the time of their follow-up assessment. This figure is higher than MCI conversion rates reported elsewhere in the literature (Busse et al., 2006, Albert et al., 2011, Petersen et al., 2014). However, the number of patients in our study with MCI is small. Almost 90% patients who are given a diagnosis of MCI will be diagnosed with dementia in the following 10 years. It is possible that the MCI patients recruited in our study disproportionately represented early MCI converters. Moreover, the average age of MCI patients in our cohort was 74.3 years. This is older than the average age for MCI diagnosis in the literature (Elias-Sonnenschein et al., 2011) and age has been shown to predict conversion from MCI to dementia in several studies (Vemuri et al., 2009, Oulhaj et al., 2009, Elias-Sonnenschein et al., 2011).

4.4.5 INFORMANT QUESTIONNAIRES

The epilepsy probable group scored significantly higher on both informant completed measures at the time of their initial study assessment. This difference persisted at the 12-month time-point, and, although the NCEE group showed a larger increase in the CDR-SOB measure, this was not significant. This suggests that the epilepsy patients attained a milestone in their decline at an early stage than the NCEE patients - best shown demonstrated by the 12-month NCEE CDR-SOB score being the same as the epilepsy possible CDR-SOB score at baseline (4.38). Whilst the difference in CDR-SOB at baseline between NCEE and the combined epilepsy groups was 1.97, at follow-up assessment this had decreased

to 1.86. This change was largely driven by a greater decline in the NCEE group (-1.01 points) than in either epilepsy group (E-Po -0.97, E-Pr -0.84).

4.4.6 E-Pr vs E-Po

At all three time points in our study (memory clinic appointment, PrESIDe baseline assessment, 12-month follow-up) the two groups in whom epilepsy was suspected were very similar. No significant differences were identified between them in terms of their ACE-III, CBI-R or CDR scores at either baseline or 12-month assessments. This is not wholly surprising as the only clinical difference between them was whether or not they had had repeated witnessed episodes or not.

4.4.7 ALZHEIMER'S DISEASE SUB-GROUP DISCUSSION

The results in the AD only cohort echo the findings of the PrESIDe cohort as a whole. This is not surprising as approximately 70% of the PrESIDe group seen at baseline and at 12-months was made up of patients with AD.

Patients with AD who experience epileptic seizures exhibit an accelerated decline in cognitive function when compared to patients with AD in whom there is no clinical suspicion of epilepsy. This is demonstrated by a fall in the mean ACE-III score from 74.02 to 72.11 (1.91 points) in the NCEE group and from 73.48 to 65.30 (8.19 points) in the combined epilepsy groups. Whilst the NCEE group had a higher ACE-III score at the time of their initial memory clinic appointment and their baseline PrESIDe assessment, the difference in scores between this group and the combined epilepsy group only became significant at the time of the 12-month follow-up assessments.

The E-Pr group scored significantly higher on the CDR-SOB at the time of their initial study assessment. This difference persisted and even increased at the 12-month time-point. Whilst the difference in CDR-SOB at baseline between NCEE and the combined epilepsy groups was 1.51, at follow-up assessment this had increased to 1.68. Likewise, the CBI-R revealed roughly twice the decline in the Comb group by comparison with the NCEE group (7.34 points vs 15.56 points) These findings again suggest a more rapid accrual of deficits in these patients,

identified by those nearest to them, and likely to increase their care requirements, and need for additional support.

4.5 CONCLUSION

The risk of epilepsy is increased in patients with dementia, of all types, and in this population epileptic seizures are associated with an accelerated rate of cognitive decline. This cognitive decline occurs across all cognitive domains measured by the ACE-III examination. The difference in the size of the decline was greatest in the attention and fluency domains of this test, suggesting that executive function is especially affected in this population. The difference between epilepsy and non-epilepsy groups is even more apparent when restricting the analysis only to patients with a diagnosis of AD, suggesting that the presence of epileptic seizures is a particularly sensitive predictor of rapid cognitive decline in these patients.

Conventional understanding regarding epileptic seizures in patients with dementia suggests that epilepsy occurs as a late-stage feature of dementia, and consequently treating seizures is unlikely to impact on the progression of disease or to result in any meaningful functional improvement for these patients. However, the findings of our study, in keeping with other recent reports (Vossel et al., 2013, Sarkis et al., 2016), suggest that epileptic seizures occur in patients at early stages of dementia and these are associated with accelerated cognitive decline. This finding should encourage clinicians to identify patients who may have experienced epileptic seizures following the onset of their memory impairment and to consider anti-epileptic medication in these patients, where not contraindicated.

The true incidence of epilepsy among patients with dementia may be even higher than I have reported. Several studies looking at the semiology of seizures in dementia, and AD in particular have recognised that seizures in this population are more likely to be focal in onset, often non-motor and rarely generalised tonic-clonic (Bernardi et al., 2010, Vossel et al., 2013, Aller-Alvarez et al., 2017). Such subtle seizures are easily missed. Several recent studies have looked at the prevalence of subclinical epileptiform activity in these patients (Vossel et al., 2016, Horvath et al., 2017, Horvath et al., 2018). In these studies prolonged EEG recording, or the use of more in-depth methods of analysis, such as

magnetencephalography have been shown to identify abnormalities even in the absence of a clinical history of seizures.

Randomised controlled double-blind studies of the effects of anti-epileptic medications in appropriately selected patients with dementia and epilepsy are required in order to evaluate whether their use can lead to a better prognosis for patients with these conditions.

Declaration:

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CHAPTER FIVE: THE SYNDROME OF TRANSIENT EPILEPTIC AMNESIA: A COMBINED COHORT OF 115 PATIENTS AND LITERATURE REVIEW

5.1 INTRODUCTION

The term *Transient Epileptic Amnesia* (TEA) was coined in 1993 to highlight the existence of a distinctive form of epilepsy causing transient amnesic attacks (Kapur, 1993). Their superficial resemblance to the attacks occurring in *Transient Global Amnesia* (TGA) warranted a related but contrasting term. Hughlings-Jackson (1888) was probably the first author to raise the possibility that transient amnesia could be the sole or most prominent manifestation of an epileptic seizure, in his description of his physician-patient, Dr Z (Hughlings-Jackson, 1888). The suggestion was supported by case reports over the following century, preceding the definition of TEA (Zeman et al., 1998). Since then, further reports have defined an epilepsy syndrome characterised by recurrent brief attacks of transient amnesia, often occurring on waking, with a probable male predominance and onset typically in middle age (Zeman et al., 1998, Butler et al., 2007, Mosbah et al., 2014).

The syndrome is of particular neuropsychological interest as the amnestic seizures are frequently accompanied by a distinctive group of persistent interictal memory complaints: accelerated long-term forgetting (ALF), autobiographical amnesia (AbA) and topographical amnesia (TopA) (Butler and Zeman, 2008b, Zeman et al., 2013, Mosbah et al., 2014). ALF is the excessively rapid loss of access, over extended intervals, to information that appears to have been acquired and stored normally over standard testing intervals of around half an hour. AbA refers to the loss of memories for all or part of one's past life: this often comes to light when reviewing family photographs or reminiscing with friends and relations, and particularly affects the rich, 'experiential' or 'autonoetic' recall of salient personal events. TopA involves difficulty in recollecting the layout of previously familiar environments, often when driving, and/or a failure to recognise previously familiar landmarks and locations. While these measurable memory problems have been described in other types of epilepsy, and in other clinical contexts, they occur particularly commonly in TEA, probably reflecting the central involvement of the memory system in this condition.

However, TEA remains a controversial disorder. Through our project website (The Impairment of Memory in Epilepsy (TIME Project) http://projects.exeter.ac.uk/time/ we receive contacts from patients around the world who have self-diagnosed, often following initial misdiagnosis, or have found it difficult to locate a clinician familiar with the disorder . Initial misdiagnoses, in patients later shown to have TEA, have included TGA, psychogenic amnesia, transient ischaemic attacks, incipient dementia, and sleep inertia. The TEA-associated interictal memory deficits are also under-recognised: clinicians continue to reassure concerned patients that their memory is normal in the absence of tests of long-term retention of remote memory which can reveal otherwise undetectable but relevant memory impairments (Zeman et al., 2018). In this chapter I consolidate the scientific description of TEA by summarising my experience with the condition in a combined cohort of 115 patients, 65 recently studied ('TIME 2 cases') and 50 patients reported in a previous series ('TIME 1 cases') (Butler et al., 2007). I review relevant publications postdating an earlier review of the topic, discuss key uncertainties about TEA in the context of a novel disease model and point to important questions for future research.

5.2 MATERIALS AND METHODS

5.2.1 PARTICIPANTS

5.2.1.1 PATIENTS

Cases of TEA were recruited to the TIME (The Impairment of Memory in Epilepsy) study, using Zeman and colleagues' 1998 diagnostic criteria (Zeman et al., 1998):

(1) A history of recurrent witnessed episodes of transient amnesia;
(2) Cognitive functions other than memory are intact during typical episodes as observed by a reliable witness;
(3) Other evidence for a diagnosis of epilepsy. This can be provided by any combination of:

(a) Epileptiform abnormalities in EEG,

(b) The concurrent onset of other clinical features of an epileptic seizure (e.g., lip-smacking and olfactory hallucinations), or

(c) A clear-cut response to antiepileptic drugs.

Patients in TIME2 were either referred to the study via a consultant neurologist (n = 53), or self-referred (n = 12) after reviewing our project website (https://projects.exeter.ac.uk/time/). In this study we include only participants referred to our study who were available for clinical and – in most cases – neuropsychological assessment in the UK.

The study was approved by the Multicentre Research Ethics Committee, United Kingdom (MREC 03/10/77). All patients gave written, informed consent in accordance with the Declaration of Helsinki.

5.2.1.2 CONTROL PARTICIPANTS

We draw on two sets of control data. For standard neuropsychological measures, mood measures and for the assessment of autobiographical memory, data previously collected from the 24 healthy controls recruited in the TIME1 series were used again for comparison in TIME2. For measures of accelerated long-term forgetting, where some adjustment in administration procedures occurred between TIME1 and TIME2 (see Neuropsychological Assessment below), a new cohort of controls was recruited. This involved 22 age and IQ-matched healthy adults from the Exeter and Oxford areas.

5.2.2 CLINICAL INTERVIEW

Interviews were conducted by a member of the study team. A detailed history was obtained from the patient and at least one witness. A standardised data-collection pro forma (appendix 6) was used to collect information in relevant domains (demographics, clinical features of the amnestic attacks, interictal symptoms, past medical history, past psychiatric history, epilepsy risk factors, current medications, family history). Medical case notes and correspondence were reviewed.

5.2.3 CLINICAL INVESTIGATIONS

EEG and MRI reports were requested from the referring clinical teams.

5.2.4 NEUROPSYCHOLOGICAL ASSESSMENT

5.2.4.1 STANDARD MEASURES

Participants were invited to complete a comprehensive neuropsychological assessment. This involved the same test battery as our original study, comprising measures of: general intelligence (Wechsler Abbreviated Scale of Intelligence -2 subtest version (Weschler, 1999)), anterograde memory (immediate and 30-minute delayed recall of a prose passage from Wechsler Memory Scale-III (Weschler, 1997); copy and 30-minute delayed recall of the Rey–Osterrieth complex figure (Osterrieth, 1944) (appendix 7); the Recognition Memory Test (Warrington, 1984)), language (Graded Naming Test) (McKenna and Warrington, 1980), and executive function (letter and category fluency).

5.2.4.2 ACCELERATED LONG-TERM FORGETTING

To take account of methodological recommendations made by Elliot (Elliott et al., 2014) we modified the method used to assess accelerated forgetting in our previous study (2007). In this second cohort, the threshold for learning was lowered from 90% to 80%, with no minimum number of trials (to remove overlearning), and a verbal memory 'wash-out task' was included to reduce the impact of verbal working memory on performance.

A list of 15 words (from the Rey Auditory Verbal Learning Task) (appendix 8) was presented orally over a maximum of 10 trials until at least 12 words (80% accuracy) could be recalled within a given learning trial. Upon reaching this criterion, participants were instructed to count backwards out aloud from 100 for 40 seconds, to prevent rehearsal of words and reliance upon working memory to aid recall. Recall of the words was assessed immediately following this distractor task, and at delays of 30 minutes and at 1-week (via telephone). After this last free recall trial, recognition memory was tested using the standard list of 30 words read aloud by the examiner. Although participants were not forewarned about the delayed probes participants were asked not to practice or write down the words between the face-to-face testing session and the telephone follow-up.

5.2.4.3 REMOTE MEMORY

Autobiographical memory was assessed using the Modified Autobiographical Memory Interview (MAMI) as in our previous study. This semi-structured interview requires participants to describe two events, relating to specific topics (e.g. holidays, weddings, career changes, car ownership, and hobbies) from each decade of their lives (from their 20s through to their current decade). For each event described, participants answer 5 questions designed to test their personal semantic memory (e.g. what type of car did you own in your twenties?) and then produce one detailed episodic memory (e.g. can you recall one time when you broke down or took it to get repaired / serviced?). Each episodic memory is scored out of 5, based on the scheme described by Graham and Hodges (Graham and Hodges, 1997) where a score of 0 indicates a failure to recall a relevant memory and 5 indicates successful retrieval of a specific episode in which event details are described. This generates a personal semantic score (out of 10/ decade) and an episodic score (out of 10/ decade).

5.2.5 MOOD

Self-reported symptoms of depression or anxiety were measured through the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) (appendix 9).

5.2.6 STATISTICAL ANALYSIS

Statistical analysis of data obtained through neuropsychological testing was performed using IBM SPSS Statistics 25.0. Analyses of variance (ANOVA) were conducted to compare groups' performances (TIME1, TIME 2 and controls). Planned contrasts comparing 1) TIME2 participants with controls and 2) TIME1 participants with TIME2 participants were included. We applied a Bonferroni adjustment of alpha (.05/11) = .0045 to correct for the number of neuropsychological measures compared in each instance.

To examine any change in prevalence of detected memory impairments across the two patient cohorts, a Pearson's chi-squared test was used to compare the number of cases identified in each patient cohort (where cases of memory

impairment were defined by performance 2 or more SD below the control mean on more than one neuropsychological test).

To investigate long-term anterograde memory performance, word list recall scores were compared between TIME2 and a new, matched control group (see above) via a repeated-measures analysis of variance (ANOVA), with factors of participant group (TIME2 or control) and delay interval (40 seconds, 30 minutes, and 1 week). The Huynh-Feldt correction for nonsphericity was applied, where needed. Given the differences in procedure, no direct comparisons were made between the TIME1 and TIME2 data sets.

Participants were entered into this analysis if they had satisfied the learning criterion (80% recalled) and demonstrated adequate retention over 30 minutes (recalling 8 or more words, consistent with a performance 1.5SD below the mean in a normative study (Carstairs et al., 2012).

To evaluate autobiographical memory in our second cohort, the semantic and episodic memory scores per decade from the MAMI were analysed using repeated-measures ANOVA, with between group factor of participant group (TIME2 or control) and the within group factor of decade (20s, 30s, 40s, 50s and most recent).

Only patients with an age of TEA onset >50 years were entered into this analysis, in order to compare recall from early adult decades free of the potentially confounding effect of epilepsy onset. A separate comparison of recent memory (from each individual's current decade) was also conducted. Lastly, self-reported symptoms of anxiety and depression were analysed using ANOVA to compare TIME1, TIME2 and healthy controls.

5.2.7 LITERATURE SEARCH

We performed a literature search using the following keywords: "transient epileptic amnesia" in MEDLINE, EMBASE and PSYCINFO up to September 2018. Studies published prior to 2008 were excluded as these had been analysed in a previous review article (Butler and Zeman, 2008b). Titles and abstracts were reviewed and further hand-searching using reference lists was performed to identify further published papers.

5.3 RESULTS

5.3.1 CLINICAL FEATURES IN TIME 2 PATIENTS

5.3.1.1 DEMOGRAPHICS

65 patients (51 male, 14 female) were recruited between January 2008 and April 2016. Mean age at the onset of amnestic attacks was 61.4 years (standard deviation [SD] 9.95; range, 26-77 years), and at entry into the study was 65.6 years (SD 8.67; range, 39-81 years). An illustrative case from the TIME study is provided in appendix 10.

5.3.1.2 DIAGNOSTIC CRITERIA

Table 5.1 specifies the grounds for the diagnosis of TEA in each case, summarised in Figure 5.1. TEA was the initial diagnosis in only 40% of cases (26/65). Other initial diagnoses were: temporal lobe epilepsy (18/65), TGA (10/65), “psychogenic” (5/65), transient cerebral ischemia / stroke (6/65). The median delay to the diagnosis of TEA was 4 years (mean, 4.17; interquartile range [IQR], 3–5).

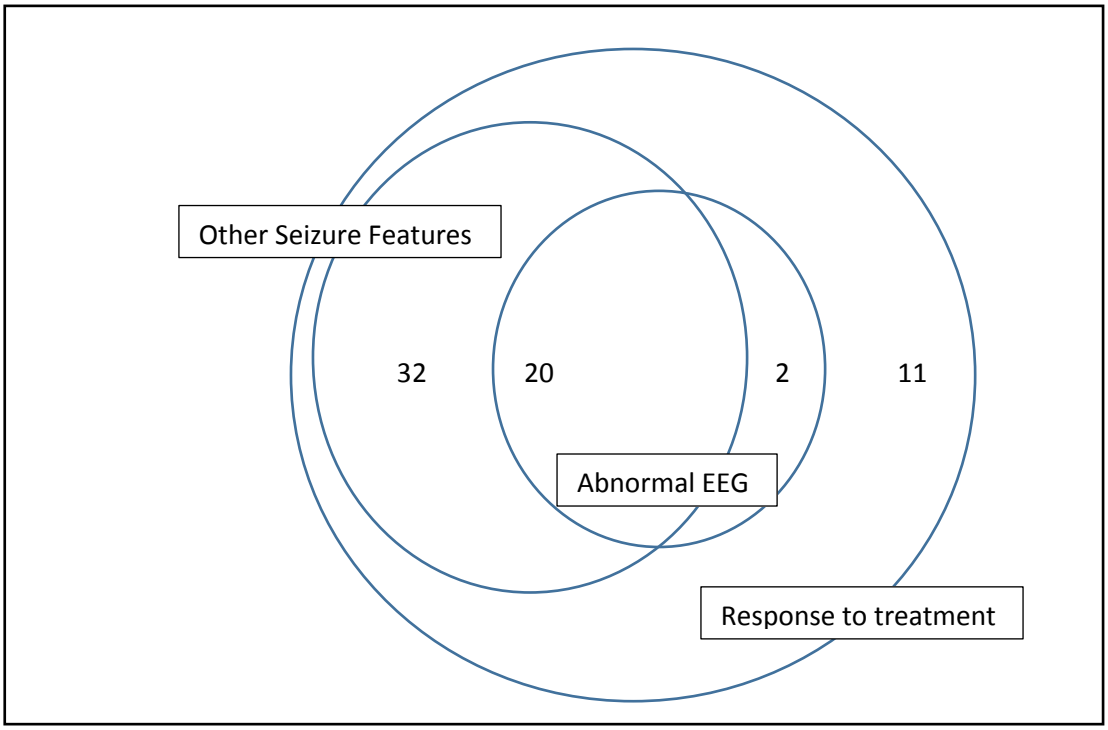


Figure 5.1: Criteria for diagnosis of TEA in TIME2 series patient

Study ID	Sex	Age at Onset (yr)	Total number of attacks	first to last attacks (mo)	Duration of attacks	Amnesia on Waking	Number of Criteria Met	EEG	Other Features sometimes Present	Treatment Response
191	M	66	10	21	5-15 minutes	Y	3	Epil	Autom, Unresp	Com
205	F	57	12	22	15-30 minutes	Y	3	Epil	Olf hall, Autom, Unresp	Com
220	M	60	36	36	15-30 minutes	Y	3	Epil	Autom, Unresp	Com
222	M	62	50	11	5-15 minutes	Y	3	Epil	Autom, Unresp	Com
235	M	61	50	64	1-5 minutes	Y	3	Epil	Olf hall, Autom, Unresp	Com
236	M	66	15	22	30 minutes to 1 hour	Y	3	Epil	Olf hall	Com
243	F	64	10	24	5-15 minutes	Y	3	Epil	Olf hall	Partial
260	M	44	175	26	30 minutes to 1 hour	Y	3	Epil	Olf hall, Autom	Com
282	F	58	200	4	5-15 minutes	Y	3	Epil	Autom, Unresp	Com
305	F	26	10		15-30 minutes	Y	3	Epil	Unresp	Com
336	M	44	50	8	5-15 minutes	Y	3	Epil	Olf hall, Autom, Unresp	Com
343	M	54	12	6	1-5 minutes	Y	3	Epil	Olf hall, Autom, Unresp	Com
358	M	47	50	76	30 minutes to 1 hour	Y	3	Epil	Autom	Com
360	M	67	20	84	30 minutes to 1 hour	Y	3	Epil	Autom	Partial

361	F	55	5	4	15-30 minutes	Y	3	Epil	Olf hall	Com
365	M	53	40	108	1-5 minutes	Y	3	Epil	Olf hall, Autom, Unresp	Partial
367	M	60	37	18	15-30 minutes	Y	3	Epil	Olf hall, Autom	Com
368	F	66	10	12	30 minutes to 1 hour	Y	3	Epil	Olf hall, Unresp	Com
375	M	72	172	22	1-5 minutes	Y	3	Epil	Autom, Unresp	Com
393	M	69	20	16	1-2 hours	Y	3	Epil	Autom	Com
195	M	59	4	37	1-2 hours	Y	2	Non-spec	Olf hall, Autom, Unresp	Com
213	F	55	24	24	1-5 minutes	N	2	Epil		Com
223	M	72	12	37	1-2 hours	Y	2	Normal	Autom, Unresp	Com
226	M	66	6	7	15-30 minutes	Y	2	Non-spec	Olf hall	Com
229	F	76	4	3	1- 5 minutes	N	2	Normal	Olf hall, Unresp	Com
232	M	66	19	36	1 -2 hours	Y	2	Normal	Autom, Unresp	Com
238	M	51	16	62	30 minutes to 1 hour	Y	2	Normal	Olf hall, Autom, Unresp	Com
241	M	52	14	7	2-24 hours	Y	2	Non-spec	Unresp	Com
251	M	66	2	23	1-2 hours	Y	2	Non-spec	Unresp	Com
254	M	66	70	16	5-15 minutes	Y	2	Normal	Autom, Unresp	Com

272	M	62	100	67	1-5 minutes	Y	2	Non-spec	Autom, Unresp	Com
277	M	63	4	14	5-15 minutes	Y	2	Normal	Olf hall	Com
288	M	69	6	86	1-2 hours	Y	2	Normal	unresp	Partial
292	M	77	30	43	15-30 minutes	N	2	Non-spec	Unresp	Com
317	F	76	50	23	1-2 hours	N	2	Normal	Olf hall, Unresp	Com
325	F	66	4	6	1-5 minutes	Y	2	Non-spec	Unresp	Com
346	F	56	15	44	2-24 hours	Y	2	Non-spec	Olf hall	Com
349	M	43	20	26	1-5 minutes	Y	2	Normal	Unresp	Com
351	M	65	24	120	5-15 minutes	Y	2	Not done	Olf hall, Autom, Unresp	Com
352	M	54	12	12	15-30 minutes	Y	2	Non-spec	Olf hall	Com
355	M	56	10	8	15-30 minutes	Y	2	Normal	Unresp	Com
356	M	67	70	70	15-30 minutes	Y	2	Normal	Autom, Unresp	Partial
359	M	65	20	33	5-15 minutes	Y	2	Normal	Olf hall, Unresp	Com
362	M	52	50	2	<1 minute	Y	2	Non-spec	Olf hall, Unresp	Com
371	M	71	6	1	30 minutes - 1 hour	Y	2	Non-spec	Olf hall	Com
373	F	70	12	56	15 -30 minutes	Y	2	Epil		Com

374	M	66	4	6	1-2 hours	Y	2	Norm	Autom	Com
378	M	65	14	45	15-30 minutes	Y	2	Normal	Olf hall, Autom, Unresp	Com
379	M	69	8	12	30 minutes to 1 hour	Y	2	Non-spec	Olf hall, Unresp	Com
380	M	58	6	5	5 - 15 minutes	Y	2	Non-spec	Olf hall, Autom	Com
383	M	59	13	48	2-24 hours	N	2	Normal	Olf hall	Com
388	M	67			1-2 hours	Y	2	Non-spec	Olf hall, Autom	Com
394	M	72	9	10	15-30 minutes	Y	2	Not done	Autom, Unresp	Com
396	M	73	8	8	1-2 hours	Y	2	Not done	Olf hall, Autom	Com
193	M	71	15	11	1-2 hours	Y	1	Non-spec		Com
207	M	63	4	21	15-30 minutes	Y	1		Not done	Com
217	M	72	2	1	15-30 minutes	Y	1	Non-spec		Com
218	F	42	100	84	30 minutes to 1 hour	Y	1	Normal		Com
257	M	57	50	53	2-24 hours	Y	1	Normal		Com
261	M	59	50	52	5-15 minutes	Y	1	Normal		Partial
322	M	66	2	93	15-30 minutes	Y	1	Non-spec		Com
340	F	39	5	6	1-2 hours	Y	1	Normal		Com

341	M	75	5	7	30-60 mins	Y	1	Normal	Com
363	M	71	17	18	30 minutes to 1 hour	Y	1	Normal	Com
376	M	55	6	10	15-30 minutes	Y	1	Normal	Com

Table 5.1: Characteristics of TIME2 patient cohort (“partial” indicates a >50% reduction in seizure frequency)

5.3.1.3 SEIZURE FEATURES

Duration, timing and frequency: Median attack duration was 15-30 minutes, with a wide variation (range <1minute to days) (Figure 5.2). 61/65 patients (94%) reported that at least some of their attacks occurred on waking from sleep. However, only 5 patients exclusively experienced seizures at this time. Median frequency of attacks per annum prior to diagnosis was 12 (interquartile range (IQR) 8-20). Median number of attacks experienced prior to diagnosis was 15 (IQR 6-36).

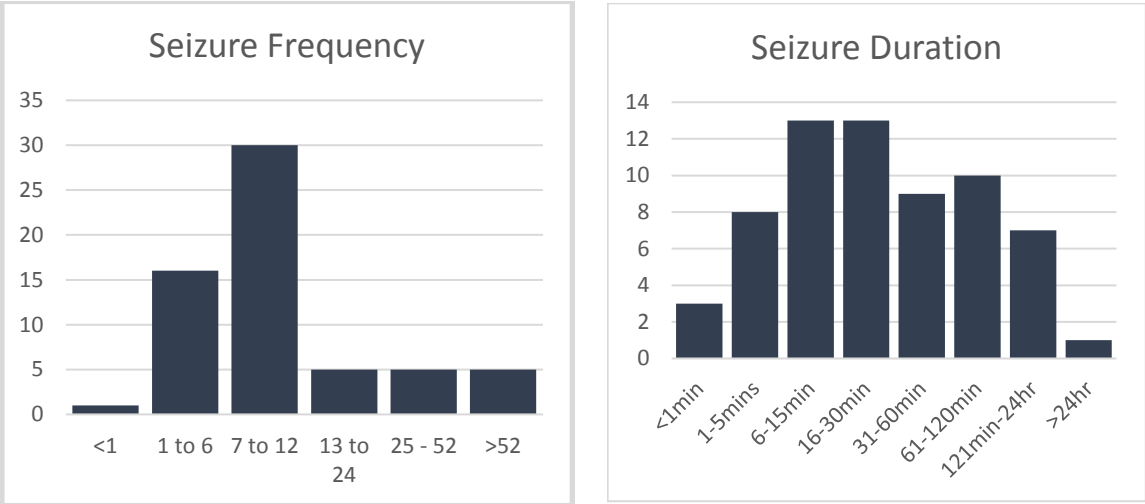


Figure 5.2: Annual frequency and duration of epileptic seizures in TIME2 group

5.3.1.4 SEIZURE TYPES

Amnesia was the sole ictal manifestation in 13/65 (20%) of patients. In 33/65 (51%) brief unresponsiveness was reported in at least some attacks. 14/65 (22%) reported an epigastric aura. 29/65 (45%) described olfactory hallucinations, and the same percentage motor automatisms, most commonly (11/65, 17%) repetitive chewing or swallowing movements. Tonic-clonic seizures occurred in only 7/65 (11%) and were typically isolated or rare events.

Ictal amnesia: 35/65 (54%) patients were able, on some occasions at least, to 'remember not being able to remember' – i.e. had partial recall of their transient amnestic episodes. Repetitive questioning during episodes occurred in 41/65 (63%) cases.

Treatment: All patients were started on anticonvulsant medication, 92% reporting complete cessation of attacks. The most commonly used final medications were Lamotrigine (31/65; 48%) followed by Levetiracetam (14/65; 22%), carbamazepine and sodium valproate (10/65 or 15% each). Topiramate was used in 3 patients (3/65, 4.6%) and Zonisamide was used in one patient (1/65, 1.5%). Drug changes were required in 24 patients, either due to inefficacy or side effects of the initial medication. Final mean daily doses were: Lamotrigine 145mg (50mg – 300mg), Levetiracetam 1182mg (500mg to 3000mg), Carbamazepine 650mg (300mg – 1600mg), Sodium valproate 850mg (400mg -2400mg), Topiramate 100mg (50mg-150mg), Zonisamide 400mg (400mg).

5.3.1.5 INTERICTAL FEATURES

AbA: 57 patients (88%) reported AbA, ranging from patchy losses for the previous 1-2 years to loss of memories up to 30 years in to the past. These forgotten episodes were frequently noted in conversation with friends and family and typically included shared experiences such as wedding, holidays and birthdays.

ALF: 48 patients (74%) reported ALF, either without prompting or when asked if they had experienced memories fading more quickly that they would typically expect over hours to weeks.

TopA: 47 patients (72%) reported TopA.

Olfaction: 29 patients (45%) reported olfactory hallucinations. 16 (25%) reported a reduction in their sense of smell. Overall 34 patients (52%) reported olfactory symptoms of some kind.

Emotionality: 26 patients (40%) reported a state of emotional lability, principally involving a tendency for sadness/tearfulness to be provoked by relatively minor stimuli (24/26), and sometimes also a feeling of increased irritability (4/26).

5.3.2 INVESTIGATIONS

5.3.2.1 MRI RESULTS

58 participants underwent a clinical MRI scan. Abnormalities were detected in 4 patients: (1) high signal in the right hippocampus; (2) frontal encephalomalacia secondary to previous brain injury, (3) slight signal change in both hippocampi

and (4) small cystic lesion on right caudate with small area of gliosis right lateral ventricle and left posterior frontal lobe.

5.3.2.2 EEG RESULTS

61/65 (94%) patients had undergone interictal EEG (Figure 5.3). Overall, 22/61 (36%) were epileptiform, 16/61 (26%) showed borderline abnormalities, 23/61 (38%) were normal. Epileptiform discharges localised to the temporal lobes, primarily, or solely, in the left hemisphere in 13/22, right-sided in 6/22, bilateral in 4/22. Non-specific abnormalities most often involved theta activity, usually localised to the temporal lobes (11/16). Other abnormalities included a single sharp wave (n=5) or a single sharp-slow complex (n=2). These findings were more often bilateral (7/16) or right-sided (6/16) than left-sided (3/16).

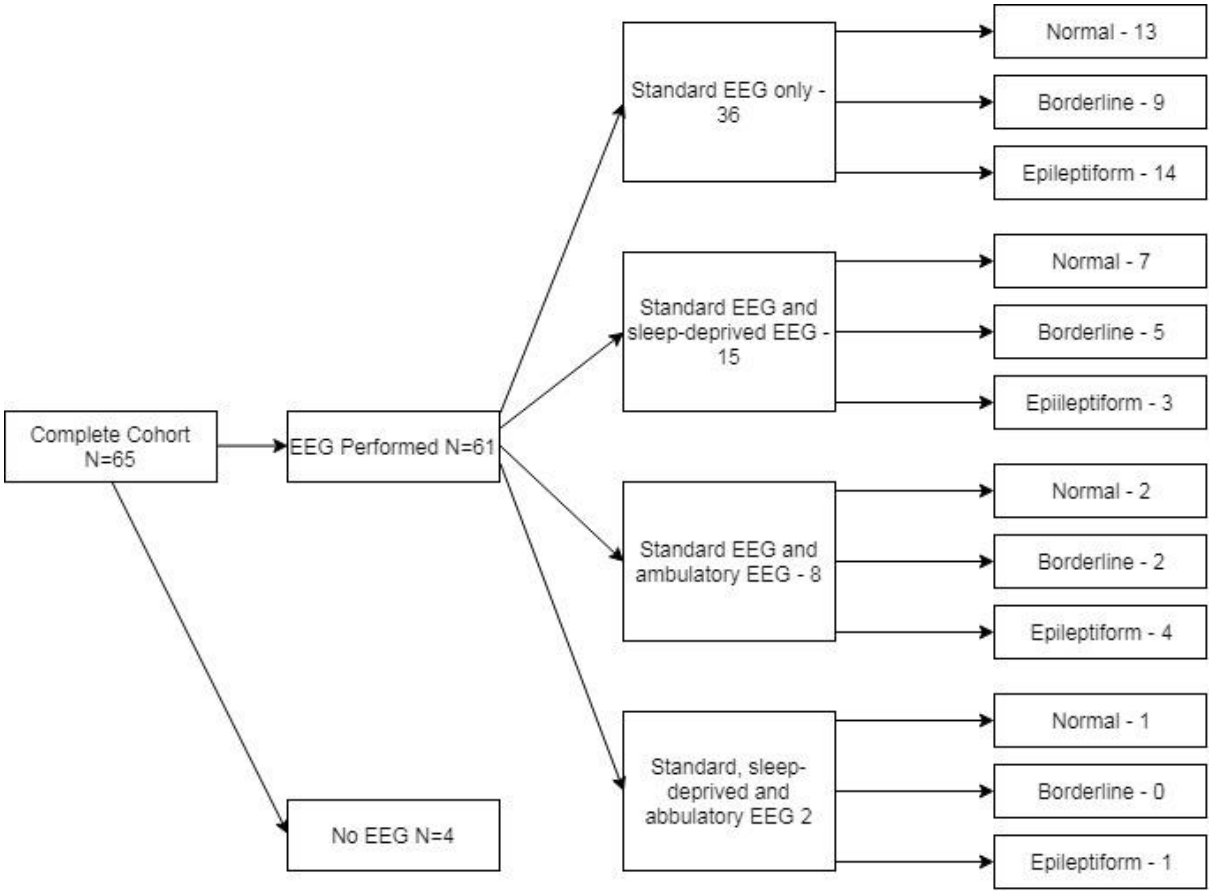


Figure 5.3: EEG flow-chart for TIME2 cohort (in cases where multiple EEGs were performed, the final test listed provided the epileptiform result)

5.3.3 COMPARISON WITH CLINICAL FEATURES IN TIME 1 SERIES

Table 5.2 presents the clinical features in the current series, our previous series and the two series combined.

Core Clinical Features of TEA	TEA 2007 (n=50)	TEA 2017 (n=65)	P value	TEA combined (n=115)
Demographics				
Mean age at onset (yr)	62.1 (range 44-77) (SD 9.1)	61.4 (26-77) (SD 9.95)	0.872	61.7 (26-77)
Mean age at presentation (SD)	66 (SD 9)	65.6 (SD 8.67)	0.150	66.7
Sex distribution (M/F)	34/16	51/14	0.207	85/30
Seizure Characteristics				
Median number of attacks prior to diagnosis	10 (IQR 6-30)	15 (IQR 6-36)	0.263	12 (IQR 6-25)
Median frequency of attacks (per year)	12 (IQR 5-20)	12 (IQR 8-20)	0.953	12 (IQR 5-12)
Median attack duration	30-60 minutes (range <1 minute to days)	15-30 minutes (range <1 minutes to days)		15-30 minutes (range <1 minutes to days)
Cessation of attacks on AED	96%	91%	1.101	93%
Amnesia sole manifestation of a seizure	28%	20%	0.318	23.5%
Tonic-clonic seizures	4%	10.7%	0.186	7.8%
Some attacks on waking	74%	94%	0.003	85%
Partial amnesia for attack	56%	54%	0.840	55%
Repetitive questioning	50%	63%	0.164	57%
Olfactory hallucinations	42%	45%	0.749	43%
Motor automatisms	36%	45%	0.333	41%
Brief unresponsiveness	24%	50%	0.005	39%
Interictal features				
c/o autobiographical memory loss	70%	88%	0.017	80%
c/o accelerated forgetting	44%	74%	0.001	61%
c/o topographical memory loss	36%	72%	<0.001	56%
Emotionality	18%	40%	0.011	

Investigations				
Interictal epileptiform activity on EEG	36%	33%	0.656	30.6%
Structural lesion on MRI	2%	7%	0.124	4.6%

IQR = interquartile range; AED = antiepileptic drug; c/o = complaint of; AML = autobiographical memory loss; TEA = transient epileptic amnesia; c/o = complains of; EEG = electroencephalogram; MRI = magnetic resonance imaging; where there is a significant difference between groups ($p<0.05$) this is highlighted.

Table 5.2: comparison of key features in TIME1 and TIME2

5.3.3.1 DEMOGRAPHICS

Age at onset and sex ratio were consistent between the two series. .

5.3.3.2 SEIZURE FEATURES

Duration, timing, frequency: Seizure duration and frequency were similar in the two series. Seizures on waking were reported more commonly in TIME2.

Seizure types: The frequency of pure amnestic seizures, repetitive questioning, olfactory hallucinations, motor automatisms and tonic clonic seizures was similar in the two groups. Brief episodes of unresponsiveness were reported more commonly in TIME2 than TIME1.

Ictal amnesia: Partial recollection of attacks occurred with similar frequency in the two groups.

Treatment: Over 90% of patients in both series reported complete cessation of seizures following the initiation of medication.

5.3.3.3 INTERICTAL FEATURES

AbA, ALF, TopA: These interictal features of TEA were reported more commonly in TIME2.

Emotionality: Increased emotionality was reported more commonly in TIME2 than it had been in TIME1.

5.3.3.4 INVESTIGATIONS

EEG and MRI abnormalities were seen with similar frequency in the two series.

5.3.4 NEUROPSYCHOLOGY

5.3.4.1 STANDARD NEUROPSYCHOLOGY

Neuropsychological test results for patients in TIME1, TIME2 and control participants are shown in Table 5.3. While full assessments were conducted in 56 participants, three were excluded from analysis given other neurological history which may have confounded test performance (one because of significant head injury resulting in structural changes evident on MRI; and two because of vascular events evident on MRI).

Neuropsychological Measure	TIME2 (n=53)	TIME1 (n=50)	Controls (n=24)
WASI (2-subtest IQ)	115.7 (14.8)	118.3 (12.8)	120.0 (14.4)
Graded Naming Test (/30)	21.5 (4.8)	21.4 (5.1)	23.5 (4.2)
COWAT (letters F,A,S)	41.8 (13.6)	42.5 (13.9)	43.8 (11.4)
Animal fluency	19.5 (6.9)	19.3 (5.9)	22.0 (4.4)
RCFT – copy (/36)	33.5 (3.5) * [a]	34.5 (3.1)	35.5 (1.1)
LM (Story 1) – Immediate (/25)	11.5 (4.1)** [b]	14.0 (4.3)	15.9 (3.8)
LM (story 1) – Delay (/25)	9.1 (4.7)**	11.7 (5.0)*	14.7 (3.8)
LM (Story 1) – Recognition (/15)	12.1 (2.0)**	12.9 (1.4)*	13.6 (1.2)
RCFT – 30 min delay (/36)	15.3 (5.9) **[a]	15.0 (6.5)*	18.6 (6.1)
RMT – Words (/50)	43.3 (6.1)**	46.1 (4.7)*	48.3 (1.9)
RMT – Faces (/50)	39.4 (5.3)**	40.7 (5.4)**	45.1 (2.9)

* denotes a significant difference p<.05 when compared with healthy controls, ** denotes p<0.0005

Healthy control participants from Butler et al 2007

[a] based on a sample of n=50

[b] denotes a significant difference p <.004 between TEA cohorts across TIME1 and TIME2

Table 5.3: Neuropsychological test performance (Mean and standard deviation)

All three groups of participants demonstrated above average intellectual ability. There were no significant differences between TIME2 and healthy controls on

language or executive function tasks, however, significant reductions were apparent on all of the anterograde memory tasks.

5.3.4.2 ACCELERATED LONG-TERM FORGETTING

ALF testing was completed in 36 of the TIME2 participants. Three were excluded from analysis due to impaired performance on standard tests of anterograde memory (delayed story recall), 8 due to inability to meet the word list learning criterion, and 6 due to poor recall at the 30-minute interval. Nineteen TEA participants and 22 age and IQ-matched healthy controls were therefore included, subject to the same exclusions listed above (healthy control mean age = 63.82, TIME2 subset mean age = 64.77 F [1, 41] =.30, p=.59; healthy control mean IQ = 116.86, TIME2 subset mean IQ = 116.38, F [1, 41] =.87, p=.36). All participants completed between 3 and 10 learning trials, with no differences between the TEA and control groups on the total number of learning trials (F[1,40] = .58, p = .45), or average final trial score (85%; F[1,40] = .01, p =.93), suggesting an equivalent performance during the learning phase of the task.

As expected, recall performance declined over time for both TEA and control participants (see Figure 4 for mean group results), with the lowest scores generated by the TEA group at all delay intervals. Repeated measures ANOVA of recall performance confirmed a significant main effect for group (F [1, 39] = 10.46, p = .002), a significant main effect for the delay interval (F [1.5, 58.9] = 153.73, p <.001), and, importantly, a significant group x delay interaction (F [1.5, 58.9] = 6.29, p = .008). Planned contrasts to explore group differences across the time intervals, showed that while the TEA and control participants did not differ significantly from each other in their change shown between 40 seconds and 30 minute recall (F[1,39] = .03, p=.86), the degree of forgetting was greater in TEA participants compared to controls between the words recalled at the short delay intervals (40 second and 30-minute recall) and performance at the 7-day interval (F[1,39] = 7.74, p = .008) (see Figure 4).

Within the TEA group, 13participants had reported symptoms of ALF. To explore whether the group x delay interaction was only evident within these participants, additional, separate analyses were run comparing control performance firstly with TEA participants who did (ALF+) and did not (ALF-) self-report ALF (Table 5.4).

As predicted, the interaction remained significant for ALF+ patients vs healthy controls (F [1.53, 66) = 8.12, p=.002, with contrasts confirming that this effect was only significant at the final level of delay (p=.003) and not at early intervals (p=.97)); but was no longer significant when comparing ALF- patients with healthy controls (F [1.57, 40.92] = .40, p =.533, with a significant main effect for delay, but no main effect for group)(as seen in Figure 5.4).

	TEA (n=19)		HC (n=22)		ALF+ (n=13)		ALF- (n=6)	
	mean	SD	mean	SD	mean	SD	mean	SD
learning trials (n)	5.05	2.37	4.45	1.84	4.92	2.33	5.33	2.66
Max. trial score (%)	84.56	5.90	84.85	5.12	84.62	6.32	84.44	5.44
40 second score (%)	70.53	9.25	76.36	10.23	70.77	10.38	70.00	6.99
30-min score (%)	64.21	9.74	70.61	12.29	65.13	10.59	62.22	8.07
1-week score (%)	21.75	16.46	43.33	22.98	17.95	15.96	30.00	15.63

Table 5.4 Accelerated long-term forgetting performance (Means and standard deviations)

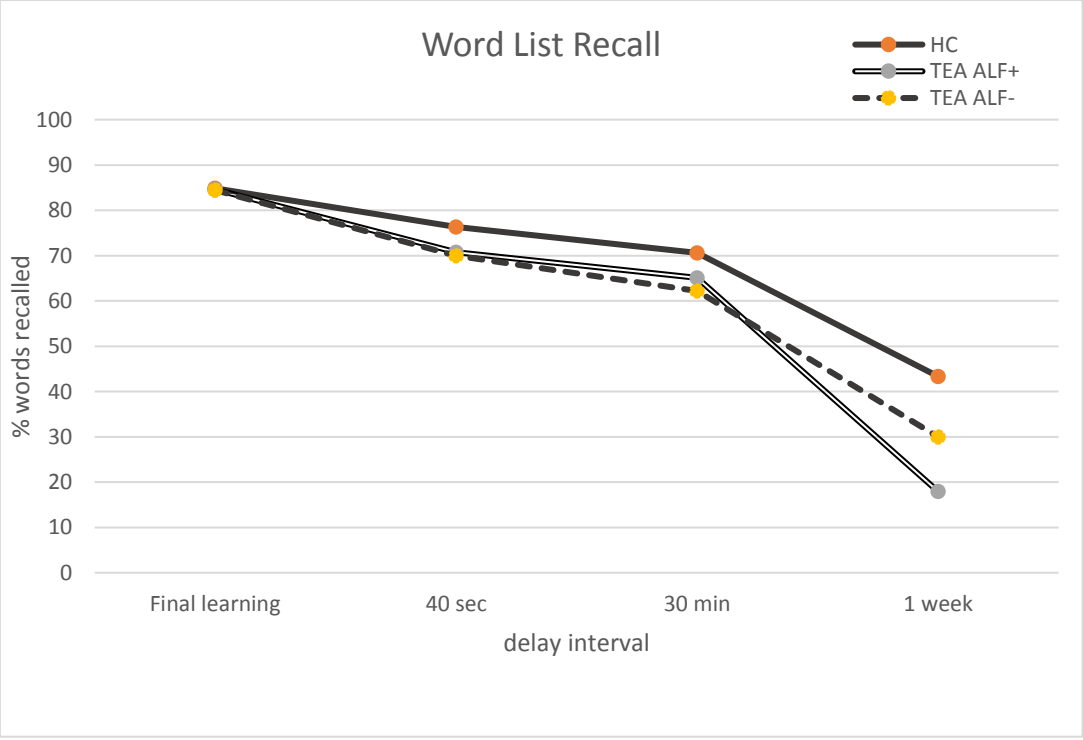


Figure 4: Mean word list recall performance of transient epileptic amnesia (TEA) patients and matched control participants over testing intervals.

Finally, to check for any associations among seizure variables (total number of seizures and frequency of seizures prior to anti-convulsants) and long term retention, Spearman's rho correlations were examined. There were no significant results (1-week retention and total seizures prior to anti-convulsants: rho = -.11, p = .662; 1-week retention and seizure frequency prior to anti-convulsants: rho = -.10, p = .749). We note, however that, patients were seizure-free at the time of testing.

5.3.4.3 AUTOBIOGRAPHICAL MEMORY

The MAMI was conducted with 24 TEA participants (17 M, 7 F) from TIME2 who met the criteria of TEA onset from age 50 years onwards. TEA participants were age and IQ-matched with 18 healthy controls from TIME1 (TEA mean age = 67.83, control mean age = 68.17, p=.881; TEA mean IQ = 120.08, control mean IQ = 121.50, p=.735).

Figure 5.5 shows the mean scores by decade for the two groups. For the personal semantic memory component of the test, repeated measures ANOVA revealed a significant main effect for decade (F[2.68, 104.61] = 5.758, p=.002). This followed a quadratic function (F[1, 39] = 10.92, p =.002) such that memories for the 20s and 50s were better recalled than for the middle decades. A significant main effect was also found for group (F[1,39] = 20.98, p<.001), with average personal semantic recall for controls slightly higher, at 9.58 out of 10, as compared with 8.53 out of 10 for TEA participants. However, no decade x group effect (F [2.68, 104.61] = 2.65, p =.059) was observed, indicating that the pattern of performance of TEA participants, while lower, mirrored that of the controls.

Similar results were found in the episodic domain. A significant main effect arose for decade (F[3,117] = 4.39, p=.006), again with contrast testing confirming a quadratic relationship where memories from the 20s and the 50s were better recalled that those from the middle periods (F[1, 39] = 11.95, p =.001). The main effect for group was also significant (F[1,39] = 45.20, p<.001), with average episodic recall remaining high for controls at 9.14 out of 10, but dropping to an average score of 6.23 out of 10 for TEA participants. The decade x group effect

was not significant (F[3,117[= .87, p =.457), indicating that the overall pattern of performance across the decades was similar for the two groups.

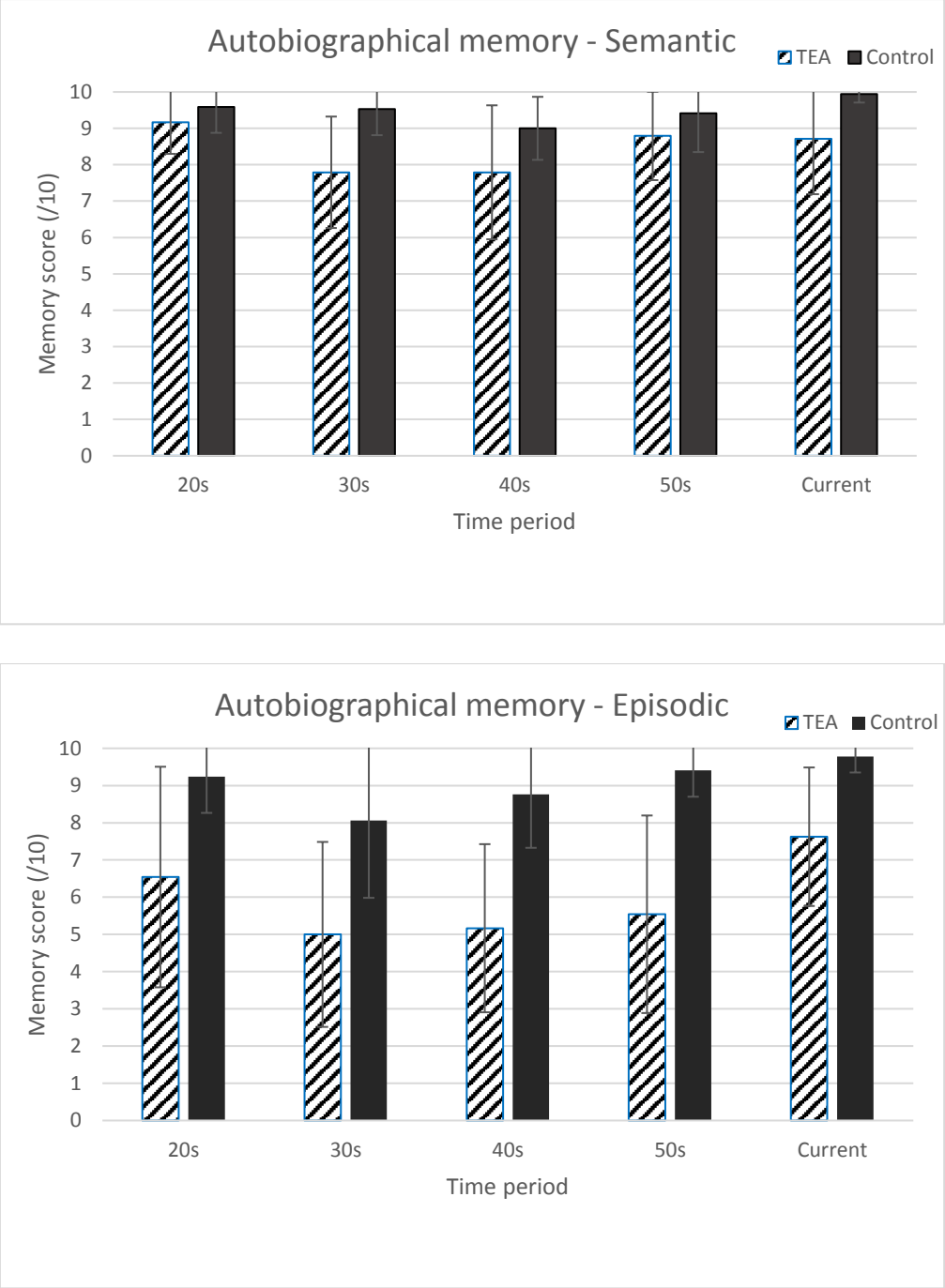


Figure 5.5: Mean scores on the Modified Autobiographical Memory Interview (MAMI) for transient epileptic amnesia (TEA) patients and matched control participants over decades. Error bars are standard deviations.

To determine the proportion of TEA participants who at an individual level showed impaired performances at each decade, cut-off scores were calculated using the threshold of 2 SDs below the control mean. The most recent decade showed the greatest frequency of impairment (17/23, 74%), followed by the 20s (14/23, 61%), 40s, (13/23, 56%), and 30s (10/23, 44%). Only 2 participants (13%) were not classified as impaired on any of the examined decades. Thus, impairments were across the lifespan, but most prevalent for memories formed post TEA-onset.

Finally, to check for any associations among seizure variables (total number of seizures and frequency of seizures prior to anti-convulsants) with overall autobiographical memory performance, Spearman's rho correlations were examined. There were no significant results (Average MAMI and total seizures prior to anti-convulsants: rho = -.11, p = .662; Average MAMI and seizure frequency prior to anti-convulsants: rho = -.10, p = .749).

5.3.4.4 MOOD

Participants reported relatively few symptoms of anxiety or depression (TIME2 mean anxiety =6.5; SD = 4.2; TIME2 mean depression = = 3.7 SD =3.1). There were no significant differences between the 3 groups (TIME1, TIME2 and controls) for either anxiety (F [2,119] =2.26, p=.108) or depression (F [2,118] = 2.61, p = .078), with all groups reporting mean levels below the standard clinical cut-offs (<8).

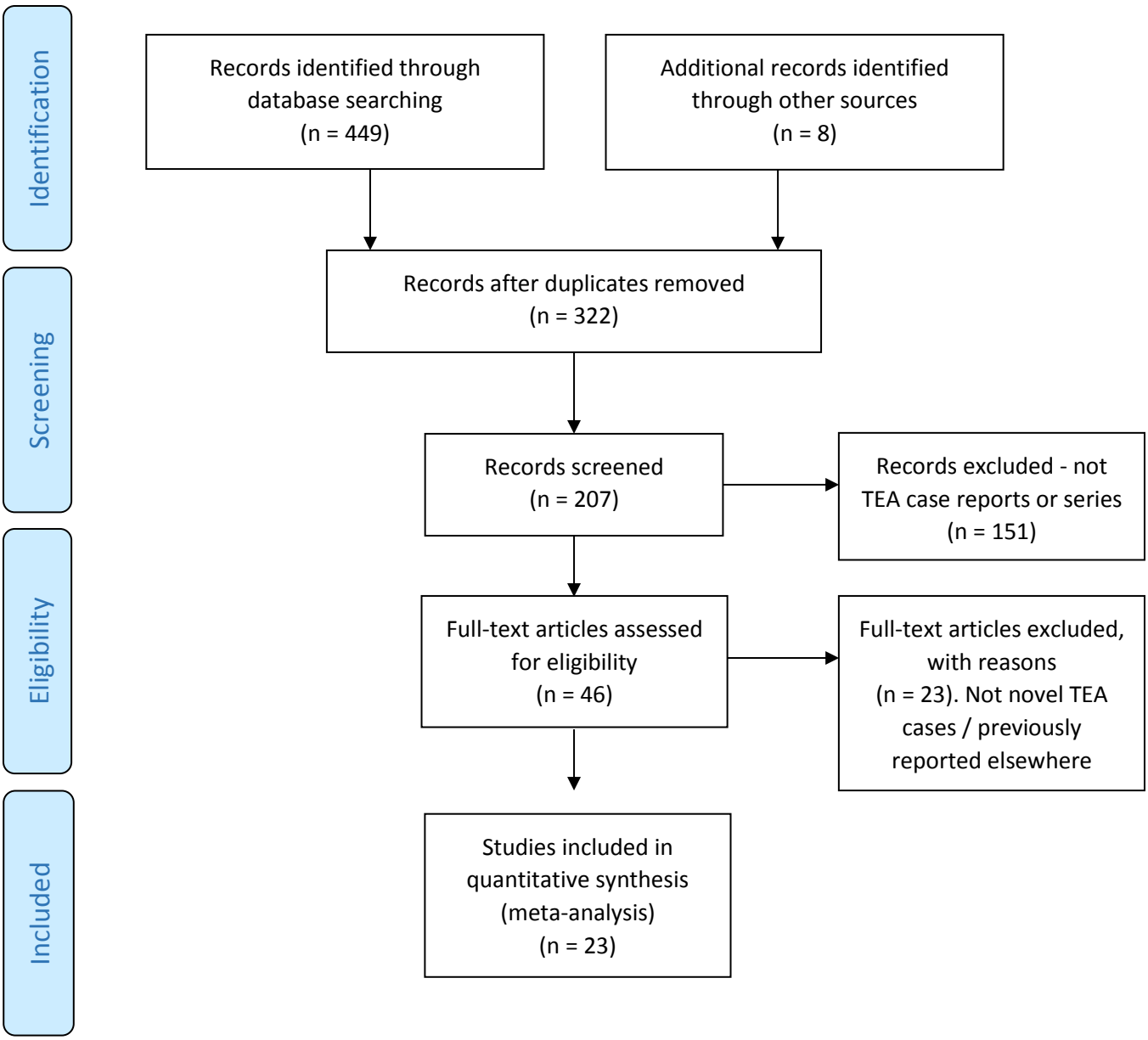
5.3.5 COMPARISON WITH NEUROPSYCHOLOGICAL FEATURES IN TIME 1 SERIES

Performance of TIME1 and TIME2 cohorts was similar on standard neuropsychological tests except that the TIME 2 group performed more poorly on the immediate recall of a short story (p <.001). At the individual level, a third of TIME2 participants (34%) showed significant memory impairment (>2 SDs below the control mean on 2 or more memory tests). Although a slightly higher number than observed in the TIME1 cohort (28%), the difference was not significant (n = 103;χ^2 = .427, p =.531). Thus the findings of standard neuropsychological tests of TIME 1 appeared largely replicated in this second cohort.

5.3.6 LITERATURE REVIEW

Using the search term 'Transient Epileptic Amnesia' we identified 322 publications between 2008 and 2018, after deduplication (Figure 5.6). The results were filtered to include only case series and case reports of novel cases of TEA this yielded in total, 115 patients with TEA from 23 studies which are summarised in Table 5.5, excluding the cases from our previous and current studies. All cases satisfied the Zeman criteria for TEA. The relatively small number of larger case series (only 4/23 studies included >3 patients) and the heterogeneity of research methods utilised precluded a systematic review of the literature. A literature review is reported in order to best capture the combined reported cases of TEA.

Figure 5.6: Flow diagram demonstrating study selection process



Author	Year	N=	M	F	mean age (onset)	mean age (diagnosis)	duration of attacks	Attacks on waking	Ictal AA	Olf Hall	Automatisms	Unresp	EEG (epileptiform changes)	Imaging	Response to AED
Huang	2008	1	1	0	67	67	5 hr						L	poss metastatic tumour L TL	
Hornberger	2010	1	0	1	43	44	<1min			no	no	no	R	MRI normal	Complete
Razavi	2010	1	1	0	67		A few minutes						B	MRI normal	Complete
Ioannidis	2011	3	1	2	53, 62, 73	54, 65, 75	30-45mins	Yes (in 2)	yes	yes x1	no	no	R	R TL angioma, R ant choroidal aneurysm, MRI normal	Complete
Favre	2011	1	0	1	60	70	30-60		yes				R	MRI normal	Complete
Soper	2011	1	0	1	45	47	1-15mins		yes		manual	no	R	asymm HC	Complete
Walsh	2011	1	1	0	55	59		yes		no	no	Yes	L	MRI normal	No
Kemp	2012	1	1	0	20-year history	73	1-10mins	yes	yes		oral			MRI normal	Complete
Mosbah	2014	30	18	12	59 (43-77)		<5 mins - >1hr	in 23%	In 20%	2/30	oral in 4/30	2/30	17/30 ep.	normal in 70% (R PL meningioma, R hemisphere ischaemic sequelae, atrophy (cortical, R hippocampal), hyperintensity (bilat hippocampal, R amygdala)	Complete in 19 (73%) of 26 cases, >50% reduction in seizure frequency in the remaining cases (27%).
Lapenta	2014	11	7	4	54.9 (35 to 78)	59.7yrs	2-10mins		yes	1/11	oral in 1/11	3/11	7/11 ep.	MRI normal in 3, 5 MTL signal abnormalities	Complete in 10/11
Del Felice	2014	3	3	1		71.25 (67 to 75)	1min-1hr		yes (in 2)	yes	oral	1/3	N	subtle MTL atrophy	Complete
Nicastro	2014	1	0	1	79	79	90mins	yes	yes		no	No	B	MRI normal	Complete
Cretin	2014	1	0	1		64	20-60mins		yes		oral + manual	Yes	N	CT and MRI normal	Complete

Woollacott	2015	1	0	1	74	76	1hr	yes	yes		oral	Yes	L	CT - TL atrophy	Levetiracetam - no, Lamotrigine - complete
Sugiyama	2015	1	0	1	75	5 months later	30mins	yes	yes	no	no	Yes	B	MRI -small hyperintense lesion in R TL	Complete
Cunha	2016	3	0	3		74, 67, 70							L	MRI normal	
Fouchard	2016	1	0	1	63	68	1-2hrs	yes	yes		no	No	L	MRI - enlarged hippocampal volume	Complete
Cho	2017	2	1	1		77, 63	10-20mins	yes	partial		no	No	R	MRI normal	Complete
Burkholder	2017	2	0	2	12 -18 months	50, 59	2-8hrs	yes	yes			1/2	B	MRI normal	Complete
Sekimoto	2017	1	0	1	6/12 earlier	67	15mins	yes	yes	no	no	no	R	MRI normal	Complete
Ukai	2017	1	0	1		67		yes			no	yes	B	MRI normal	Complete
Ramanan	2018	31	20	11		median age 70							20/31 ep.	6/31 focal abnormalities, not further specified	100% improved with AEDs
Lanzone	2018	15	4	11	67.2 (59-75)		20mins - 24 hrs	in 40%	yes				IEA in 15/15 on 24hr EEG	MRI normal in 11/15 (thalamic cavernoma, cystic pinealoma, bifrontal post-traumatic lesion, L TL venous ectasia)	complete in 8/15, partial in 5/15

Table 5.5: features of TEA studies included in review (in order of publication date) Key: AA=anterograde amnesia, Olf hall=olfactory hallucination, Unresp= unresponsive episodes, EEG=electroencephalogram, L=left, R=right, B=bilateral, N=normal, HC=hippocampus, GBM= glioblastoma multiforme, TL=temporal lobe, PL =parietal lobe, CVD= cerebrovascular disease, IEA= interictal epileptiform abnormalities, blanks indicate information unavailable/not reported.

5.3.6.1 CLINICAL FEATURES: DEMOGRAPHICS

Summing across these studies, the sex ratio was equal (male 58, female 57), though three of the four larger series reported a male preponderance (Lapenta et al., 2014, Mosbah et al., 2014, Ramanan et al., 2018). The mean age of onset for TEA has been reported as 59, 67.2 and 54.9 years in the three larger series providing this information, with onset age ranging from 35-78 years. The reported interval between symptom onset and diagnosis ranges from around 6 months to 6.2 years.

5.3.6.2 SEIZURE FEATURES

Duration: The majority of reported episodes fall between a few minutes and one hour, but there is extensive variation with seizure episodes lasting from less than one minute (Hornberger et al., 2010) up to 24 hours (Lanzone et al., 2018),

Timing: 13/23 (57%) studies included in this review describe episodes of TEA occurring on waking in 27/60 (45%) patients.

Frequency: The frequency of TEA attacks ranges from several times per week (Soper et al., 2011) to less than once per year (Burkholder et al., 2017). Comparable data are available for 15/23 studies listed above (46/114 cases). In this group 6/46 (13%) report at least one seizure per week, 17/46 (37%) report seizures at least once per month but less than weekly, and 23/46 (50%) describe less that one seizure per month.

Seizure types: Pure amnestic seizures are described in between 17% (Mosbah et al., 2014) and 64% (Lapenta et al., 2014) of patients. Brief unresponsiveness is reported in a total of 9/23 studies. 12/51 (23.5%) cases presented by these studies describe this phenomenon. An epigastric aura is described in 3 studies (Ioannidis et al., 2011, Kemp et al., 2012, Cretin et al., 2014) and orofacial automatisms in 4 (Ioannidis et al., 2011, Kemp et al., 2012, Cretin et al., 2014, Burkholder et al., 2017). Generalised tonic-clonic seizures are uncommon (10% in Mosbah (2014), 9% in Lapenta (2014). In one case (Walsh et al., 2011), persistent generalised tonic-clonic seizures were resistant to anti-epileptic treatment leading to a temporal lobectomy.

Treatment: Patients with TEA respond well to treatment with anti-epileptic medication. 94/96 cases (97.9%) in whom the response to anti-epileptic treatment was reported describe a reduction in the number of seizures following initiation of medication. In 59 of these patients this is documented as being complete seizure cessation, and in 12 this reduction is described as partial (>50% reduction in seizures). Ramanan (2018) states that all 22/31 patients for whom follow-up was available improved - although it is not clear whether this represents a partial or complete improvement (Ramanan et al., 2018).

5.3.6.3 INTERICTAL FEATURES

The interictal features described in TEA have not been routinely assessed in either case studies or case series of TEA patients and are therefore not as thoroughly described. Findings in studies where these features have been investigated are described below.

AbA: 13/23 studies included in this review describe interictal autobiographical memory impairments. Mosbah et al. (2014), report that retrograde memory loss is greater for the episodic than the semantic component of autobiographical memory. Recent memories were especially severely affected, with measurable improvement in autobiographical memory for events from the past five years following treatment (Mosbah et al., 2014).

ALF: 9/23 studies describe the presence of ALF in TEA, in 25 patients. In studies with multiple patients, this feature was described in 16/30 (53%) (Mosbah et al., 2014), 1/3 (33%) (Ioannidis et al., 2011, Del Felice et al., 2014) or 1/2 (50%) (Burkholder et al., 2017), giving a total of 18/35 (51%).

TopA: TopA is described in only 2/23 studies (2 patients); described as either ‘a tendency to lose her way even in familiar locations’ (Woollacott et al., 2015) or simply as ‘topographical amnesia’ (Ioannidis et al., 2011). None of these studies measured topographical memory formally using neuropsychological tests.

Olfaction: A decreased sense of smell, occurring in the setting of TEA was described in only 1 study (1 patient) (Ukai et al., 2017). 1/3 cases described by Ionnaidis (Ioannidis et al., 2011) features reports of ‘strange and bad smells’ as an element of seizure episodes.

Emotionality: 2/23 studies describe a clear change in the emotional character of their patients with TEA. In one case this change was becoming angry and short-tempered (Ukai et al., 2017), and in the other low mood and depression was reported (Cretin et al., 2014).

5.3.6.4 INVESTIGATIONS

EEG: The rate of EEG abnormalities reported in published case series has exceeded 50% (57% (Mosbah et al., 2014) 64% (Lapenta et al., 2014)). EEG abnormalities have also been common in TEA case reports, most often occurring in the right temporal or frontotemporal leads (Hornberger et al., 2010, Ioannidis et al., 2011, Soper et al., 2011, Milton et al., 2012, Cho et al., 2017) although abnormalities are also frequently found on the left (Walsh et al., 2011, Fouchard et al., 2016), and bilaterally (Rabinowicz et al., 2000, Mendes, 2002).

MRI: In the largest TEA case series, the majority of participants have normal MRI scans (25/31 (Ramanan et al., 2018), 21/30 (Mosbah et al., 2014) 11/15 (Lanzone et al., 2018). Of the 110 cases where MRI results were reported, 72.7% were normal. Where MRI abnormalities have been described, these have most commonly involved the temporal lobes (14/30), with findings including mesial temporal lobe signal abnormalities (Lapenta et al., 2014), right temporal cavernous angioma (Ioannidis et al., 2011), a small hyperintense lesion in right hippocampus (Sugiyama et al., 2015) and enlarged hippocampal volume with loss of architecture and increased hippocampal tail signal (Fouchard et al., 2016). Extra-temporal abnormalities have included bifrontal post-traumatic change (Lanzone et al., 2018), right parietal lobe meningioma (Mosbah et al., 2014) and a right anterior choroidal aneurysm (Ioannidis et al., 2011).

5.4 DISCUSSION

The substantial series of patients described here, combined with those identified in our literature review, supports the existence of a treatment-responsive epilepsy syndrome characterised by amnestic seizures, often occurring at roughly monthly intervals, typically lasting for 15-30 minutes, frequently manifesting on waking, with onset in middle age and a possible male predominance; a high frequency of interictal memory deficits, especially ALF and AbA, and – principally in our case series - both ictal and interictal olfactory disturbance with a tendency to emotional

lability, specifically easily provoked tearfulness. I will discuss in turn i) whether TEA should be regarded as an epilepsy syndrome, ii) the neuropsychological and neurobiological bases of the prominent associated interictal memory disturbance, iii) a model designed to capture current understanding of the condition and to identify key unanswered questions for future research.

5.4.1 IS TEA AN EPILEPSY SYNDROME?

There are compelling grounds for concluding that epilepsy is the underlying cause of the disorder described here. The patients we have described collectively show epileptiform changes on EEG, exhibit other clinical phenomena suggestive of epilepsy, such as paroxysmal alteration of awareness or olfactory hallucinations, and show a clear-cut response to anticonvulsant drugs. While opportunities to record EEG during an amnestic episode are exceptional, such recordings indicate that transient amnesia can occur both as an ictal and as an immediately post-ictal manifestation (Butler and Zeman, 2008a).

If the diagnosis of epilepsy is accepted in these cases, do they belong to a distinctive epilepsy *syndrome*? Epilepsy syndromes involve a ‘complex of signs and symptoms that define a unique epilepsy condition’; the complex should involve ‘more than just the seizure type’, but is distinct from an ‘epilepsy disease’, a condition with a ‘single, specific, well-defined aetiology’ (Engel, 2006). TEA precisely satisfies this definition, given its distinctive demographic features, ictal characteristics and inter-ictal manifestations. As its aetiology is varied, it is not an ‘epilepsy disease’. In this section we will consider some potential objections to this view, in particular inconsistencies between the features reported in the existing literature, the existence of atypical cases and the ‘grey zone’ between TEA and other forms of temporal lobe epilepsy. The question of aetiology is considered further in section 5.4.3.

While our two consecutive series of patients with TEA display marked commonalities, in demographic features and ictal characteristics, they differ with respect to the reported frequency of episodes on waking, interictal memory disturbance and emotional lability. In each case, the frequency of these features was higher in TIME2 than TIME1. While we attempted to gather clinical data in a consistent fashion over time, we suspect that the apparent increase in the

frequency of these features reflects increased vigilance, stimulated by our initial findings, rather than any true difference between the patient groups. However, whether or not this is the case, these modest quantitative differences between the two series do not undermine the key elements of the syndrome, outlined above.

The 115 patients described from our centre broadly resemble those reported from other centres in most respects, in particular, age of onset and seizure characteristics. The interictal neuropsychological features of TEA have been reported less frequently in other reports than in ours, but both AbA and ALF have been described repeatedly. Olfactory disturbance and emotional lability are much more common in our series than in other reports: whether this reflects a true difference, or a difference in ascertainment, is unclear.

Some cases in our current series are atypical with respect to age, length of amnesic episode, treatment resistance; one additional case reported provocation of amnesic episodes by exertion. Two cases (305, 340) presented below the age of 30, more than three standard deviations below the mean age at presentation. Case 305 satisfied all three diagnostic criteria, with attacks of typical duration; case 340 satisfied one criterion (clear-cut treatment response) with longer than usual attacks (1-2 hours); both had attacks on waking. Case 305 had experienced 26 episodes, case 340 five episodes. 4 patients (241,383, 257, and 346) had 'TGA-like' episodes of amnesia lasting more than 2 hours: three of these patients satisfied two criteria each (treatment response and the occurrence of other suggestive features, olfactory hallucinations in two cases, unresponsiveness in one), while case 257 satisfied one criterion (treatment response). All four patients had experienced more than 10 episodes, and three of the four described episodes on awakening. All four were in their fifties. 5 patients described an incomplete response to treatment (243, 360, 365, 356 and 261). Three (243, 360, 365) satisfied three criteria, while case 356 satisfied two (automatisms/unresponsiveness and treatment response, albeit partial) and case 261 satisfied one (clear-cut but incomplete treatment response). All had experienced frequent events of typical duration (<1 hour), some occurring on waking. Three patients were in their sixties, two in their fifties. One patient, an overseas patient assessed in the UK but not included in the current series, described episodes of typical duration, occurring at roughly monthly intervals,

often on waking, and gave a clear description of precipitation of episodes by exertion, a feature more often associated with TGA; some episodes were accompanied by olfactory hallucinations and video-telemetry confirmed the diagnosis of epilepsy. Thus these atypical features generally occurred singly, in patients whose characteristics were otherwise typical for TEA, with no suggestion of distinct subgroups or likely alternative diagnoses.

Finally, in some patients the clinical phenotype falls in a grey zone between 'typical' temporal lobe epilepsy and TEA. For example, patients with focal seizures with impaired awareness sometimes exhibit a period of prominent post-ictal amnesia, but these are not the key presenting feature. There is also a group of patients with temporal lobe epilepsy who present with notable interictal memory disturbance of the kind associated with TEA, accompanied by subtle seizures, but who never have amnestic events of the kind required for a diagnosis of TEA. The term 'Epileptic Amnesic Syndrome' has been proposed to accommodate patients with TLE accompanied by such interictal memory disturbance regardless of whether they do or do not also have amnestic seizures (Gallassi et al., 1992, Gallassi, 2006). The features of such borderline cases do not, however, call into question the existence of the core syndrome of TEA.

Thus TEA is a distinctive epilepsy syndrome, with substantially consistent features across the two series of patients described from our centre and in recent reports from other centres. The relatively minor inconsistencies between our two series are likely to be explained by heightened awareness of the clinical features by the time we studied our second series. The existence of 'atypical' and 'grey' cases indicates that there are areas of overlap between TEA and other related epileptic conditions, but does not invalidate the proposal that TEA is a distinctive epilepsy syndrome.

5.4.2 THE NATURE OF THE INTERICTAL MEMORY DISTURBANCE IN TEA

The majority of patients with TEA describe characteristic symptoms of interictal memory disturbance, in particular symptoms of ALF, AbA and TopA. These are often the most prominent and sometime the earliest symptoms of TEA (Hornberger et al., 2010, Jansari et al., 2010, Mosbah et al., 2014, Zeman et al.,

2018). As only ALF and AbA have been studied in detail in the context of TEA we will focus on these here.

These phenomena are now established clinical entities with operational definitions. In particular, some individuals with TEA who perform within normal limits on standard measures of memory nevertheless have measurable evidence of ALF and/or AbA in the presence of corresponding symptoms. There is, however, continuing uncertainty about their pathophysiology, specifically regarding which phase of memory processing is perturbed (see Figure 5.7) and whether the underlying cause is physiological or structural.

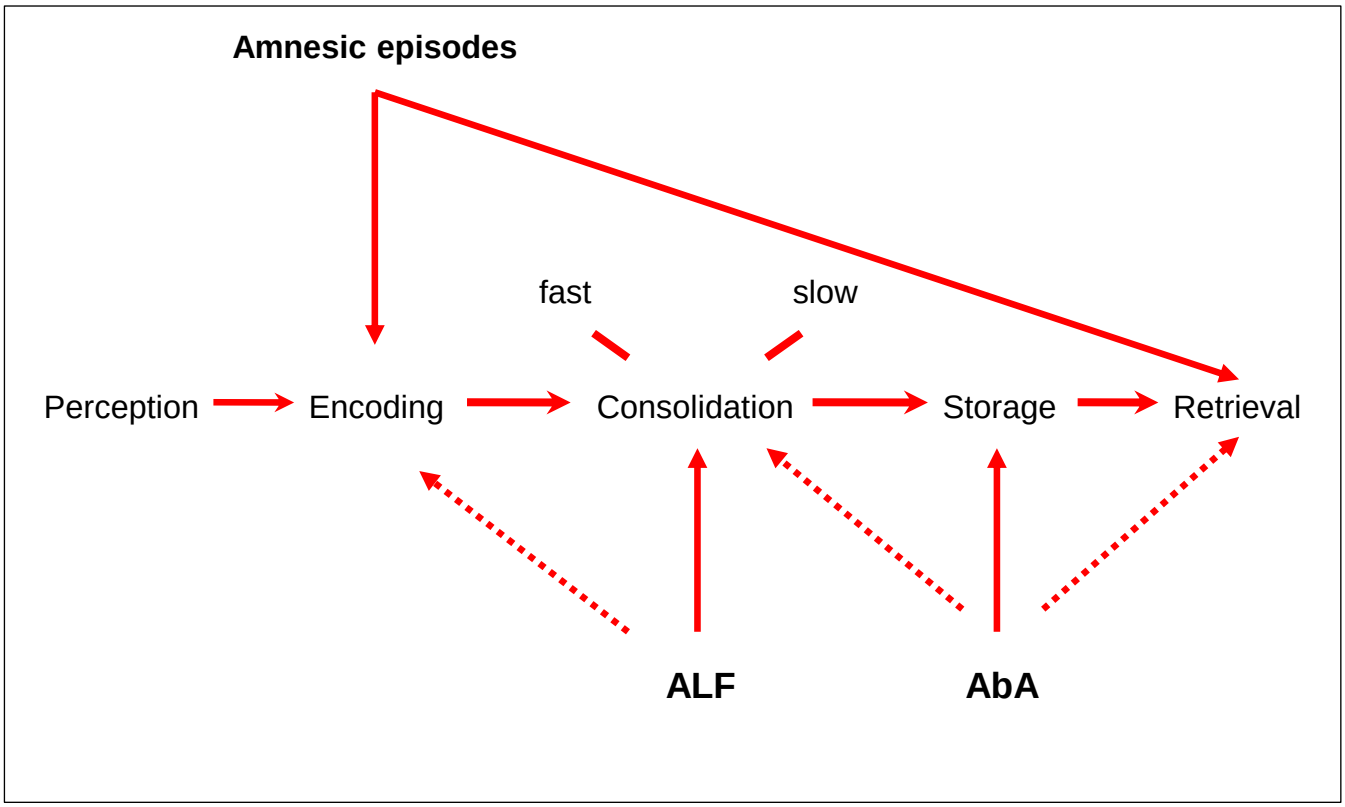


Figure 5.7: The mechanisms of the three well-studied forms of amnesia occurring in TEA in relation to the key stages of memory processing: episodes of ictal amnesia ('TEA') result from impairment of memory encoding, retrieval, or, often, both; accelerated long-term forgetting (ALF) is due to an impairment of consolidation processes, with a possible contribution from an encoding impairment; the autobiographical amnesia (AbA) probably results from memory degradation or erasure, in the case of remote memories, but loss of access,

impairing retrieval, and ALF, affecting consolidation, can also play a part. Adapted from (Zeman et al., 2012)

In the case of ALF, the presence of memory impairment at extended intervals in patients with apparently normal learning, and intact early recall, suggests an impairment of memory consolidation. This interpretation is supported by examples of patients with impeccable performance on anterograde tests at standard intervals who nonetheless show marked accelerated long term forgetting (Butler and Zeman, 2008a, Jansari et al., 2010, Tramoni et al., 2011, Witt et al., 2015, Zeman et al., 2016). Existing evidence indicates that ALF is first detectable within hours of learning (Hoefeijzers et al., 2015), and that it occurs predominantly during wakefulness rather than sleep, perhaps hinting at an increased sensitivity to retroactive interference (Atherton et al., 2014, Hoefeijzers et al., 2015). However, there is also evidence that patients with TEA show early forgetting, over standard intervals, on recognition tests using visual materials (Atherton et al, 2019; (Dewar et al., 2015), and some work in patients with TLE has suggested that ALF, in fact, flows from an impairment of memory acquisition (Cassel et al., 2016). Thus it remains controversial whether ALF reflects a true impairment of memory consolidation or rather the increasing sensitivity of memory tests at longer intervals to impairments present from, or very close to, the point of memory acquisition. We have previously suggested that this may be, in part, a false dichotomy, as such impairments will often coexist and interact (Zeman et al., 2016, Baker and Zeman, 2017).

There is also uncertainty over the relative importance of physiological factors, particularly ictal or interictal discharges versus structural factors in the causation of ALF. Studies – predominantly in patients with TLE - identifying a positive correlation between seizure frequency and ALF (Jokeit et al., 2001, Mameniskiene et al., 2006, Wilkinson et al., 2012), interictal discharge frequency and ALF (Mameniskiene et al., 2006, Fitzgerald et al., 2013), and reduction of ALF by anticonvulsant treatment (O'Connor et al., 1997, Midorikawa and Kawamura, 2007) and epilepsy surgery (Evans et al., 2014) argue for the importance of physiological factors. The apparent reversibility of ALF in some cases of TEA also points to a modifiable, physiological cause (Savage et al., 2019a). However, other studies have failed to identify such relationships (Blake

et al., 2000, Jansari et al., 2010, Muhlert et al., 2011). Moreover, ALF has recently been reported in patients with pre-symptomatic genetically determined Alzheimer's disease (Weston et al., 2018) and in children following head injury (Lah et al., 2018), suggesting that epileptiform brain activity may not be required for its occurrence. Conversely, Butler et al (Butler and Zeman, 2008a, Butler et al., 2013) found no correlation between volumes of limbic structures and the severity of ALF, arguing against a straightforward structural explanation of ALF in TEA. Thus, just as impairment of both early and later phases of memory processing are likely to contribute to ALF, so it seems likely that both physiological and structural factors may be relevant, though the evidence in TEA somewhat favours the importance of physiological disturbance. In a detailed single case study, the resolution of ALF on withdrawal of the inciting agent – high dose intrathecal baclofen - clearly demonstrated a reversible, physiological or pharmacological, cause (Zeman et al., 2016).

With respect to the AbA associated with TEA, detailed case studies indicate that TEA can erase or render inaccessible previously detailed autobiographical memories (Manes et al., 2001, Zeman et al., 2016, Zeman et al., 2018). This points to a disorder of storage, or possibly retrieval, although even rich retrieval cues failed to elicit recollection in these cases, arguing that in general storage is the more likely locus of pathology. We have, however, previously reported one patient who unexpectedly 'recovered' memories indicating that retrieval failure is, at least sometimes, the explanation for AbA in this condition (Milton et al., 2010). Finally, individuals with ALF would be expected to develop a degree of AbA over time for events occurring after the onset of ALF: the 'disappearance' of initially detailed memories, of the kind predicted by this hypothesis have been documented in the cases of CS (Zeman et al., 2016) and MB (Zeman et al., 2018). Mosbah et al (Mosbah et al., 2014) reported an improvement in autobiographical recall for recent events following treatment, in keeping with this possibility; Savage et al (Savage et al., 2019a) report a similar improvement in patient CS. Thus it is likely that AbA in TEA can reflect disorders of several stages of memory processing, including consolidation, storage and retrieval. Our working hypothesis is that the primary mechanisms of AbA in TEA, particularly in cases with temporally extensive memory loss, is degradation of stored engrams. One further possibility is worth considering, though there is at present no relevant

evidence: that the AbA of TEA is due to a problem with reconsolidation (Nader and Hardt, 2009). This could account for the close association between ALF and AbA.

Anecdotal evidence points to a role for epileptic activity in the genesis of TEA-related AbA but we have not detected a correlation between seizure frequency and duration and the severity of AbA in our patient group. The probable though controversial association between ECT, which produces iatrogenic seizures, and AbA (Fraser et al., 2008) is also in keeping with the hypothesis that TEA-related AbA is at least partly the outcome of epileptic activity propagating through the autobiographical memory network, resetting the synaptic weights on which episodic autobiographical memories are likely to depend. Although there is evidence in other contexts that structural brain damage can produce AbA, to date there is no evidence of any correlation between volume loss in limbic structures and AbA in patients with TEA. Thus the available evidence favours a role for epileptiform activity in the causation of AbA in TEA, with a possible, but so far unquantified, contribution from structural factors.

Cognitive deficits occurring in epilepsy are sometimes caused by drug treatment and by mood disturbance. However, given that both ALF and AbA can be detected in patients with TEA prior to treatment (Mosbah et al., 2014) and that there is no evidence for an elevated rate of mood disturbance in the majority of patients (Butler et al., 2007, Mosbah et al., 2014); this series), neither explanation is likely here.

In summary ALF and AbA, both common interictal features of TEA, reflect disorders of several stages of memory processing, affecting acquisition and consolidation in the case of ALF, storage and retrieval in the case of AbA for remote memories (with a contribution from ALF in the case of AbA for post-onset memories). Current evidence favours a predominant role for physiological factors in causing these phenomena in TEA, though structural factors are undoubtedly relevant in other contexts, and may also play some role in TEA.

5.4.3 A MODEL OF TEA

The aim of this section is to summarise current knowledge of TEA, identify unanswered questions and propose testable hypotheses regarding the underlying mechanisms (Figure 5.8).

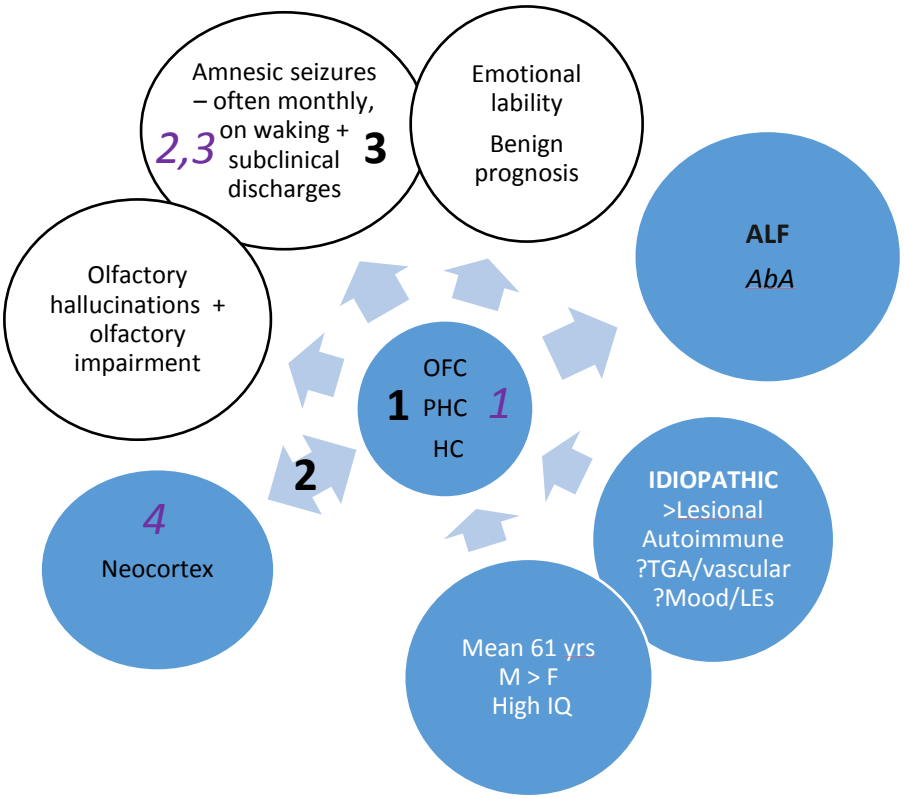


Figure 5.8: A model of TEA: white text summarises demographic and aetiological factors; the central circle highlights the limbic regions likely to contain the seizure focus; white circles summarise the key clinical features, which also include interictal memory disturbance, ALF (bold) and AbA (italic). The numbers refer to possible mechanisms for ALF and AbA (see main text for further discussion); the neocortex interacts with limbic regions in memory processing (AbA = autobiographical amnesia, ALF = accelerated long-term forgetting, HC = hippocampus, LEs = life events, OFC = orbitofrontal cortex, PHC = parahippocampal cortices (including perirhinal cortex), TGA = transient global amnesia).

5.4.3.1 AETIOLOGY

The majority of cases of TEA are idiopathic, but its typical occurrence in middle aged people, with a probable male predominance, points to an age-related susceptibility and the possible relevance of hormonal factors. Although *TGA* is unlikely to result from epilepsy in the majority of cases, the similarity in the ages of patients affected by TGA and TEA suggests that common age-related factors underlie both conditions. Rare symptomatic (lesional) cases of TEA are described and discussed further below. We have recently reported a case of TEA occurring secondary to NMDAR antibody mediated encephalitis (Savage et al., 2019b). The significance of the high IQ of the patients in our series is uncertain, but we suspect it reflects the need for an articulate description of confusing symptoms in the diagnosis of TEA. The possibility that vascular risk factors may predispose to TEA was raised tentatively in a previous case control study, with associations - on the borderline of significance after correction for multiple comparisons - between TEA and cardiac arrhythmia, valve disease and arterial aneurysm (Butler and Zeman, 2011). Some patients with TEA have an initial episode closely resembling TGA, posing the question of whether TGA can sometimes lead to TEA. Mosbah et al noted a high frequency of depression and adverse life events preceding the onset of TEA in their cases: we have encountered individual cases in which mood disorder and life events are plausible triggers, but these relationships require further systematic study before firm conclusions can be drawn. Transient amnesia has been described as a seizure type among patients with Alzheimer's disease (Vossel et al., 2013, Vossel et al., 2017), but the clinical context typically distinguishes dementia related cases of epileptic amnesia from those we have described

5.4.3.2 SEIZURE SOURCE

Manual and automated measurement of brain structures in TEA has revealed mild atrophy of limbic regions, namely bilateral straight gyrus, medial orbital gyrus, hippocampus and right perirhinal cortex (Butler and Zeman, 2008a, Butler et al., 2013). In the minority of cases with a likely structural cause for TEA, the causative lesion lies within or close to this group of regions. In a single case study with radiological localisation, an exacerbation of TEA was associated with swelling and high signal in the left hippocampus with hypermetabolism in the

same region on a 2-Fluoro-2-[18F]-deoxy-D-glucose PET scan which resolved with symptom improvement (Butler and Zeman, 2008a). This patient went on to develop left hippocampal atrophy. In cases with epileptiform interictal EEGs, or ictal recordings, the discharges are temporal or fronto-temporal, in keeping with the localisation suggested by brain imaging.

5.4.3.3 SEIZURE CHARACTERISTICS

The amnesic episodes in TEA, which typically last around half an hour, are unusually prolonged for epileptic seizures: we discuss their mechanism further below. Their occurrence on waking is in keeping with a medial temporal seizure source (Durazzo et al., 2008, Mirzoev et al., 2012). The high frequency of monthly episodes is a striking and puzzling feature, hinting at some underlying process with a similar time course involving limbic cortices, but cyclical epilepsy is described in other contexts (Cook et al., 2014, Cook et al., 2016, Baud et al., 2018). Olfactory hallucinations, sometimes prolonged, and both subjective and objective alterations in olfaction, are common in TEA, at least in our experience, and can provide a diagnostic clue.

5.4.3.4 SEIZURE MECHANISM

Surface EEG recording during an amnesic attack was performed in nine literature cases and one TIME case. All recordings showed seizure activity, which in 8/10 cases involved both temporal lobes and in the others remained unilateral (one left- and one right-sided). Amnesia was observed as an ictal phenomenon in six cases and as postictal in four cases. This suggests that the amnesia occurring in episodes of TEA can occur both as true ictal manifestations and as post-ictal phenomenon, a ‘Todd’s paresis’ of memory.

5.4.3.5 EMOTIONAL LABILITY

We noted a characteristic form of emotional lability in 18% of our first series of patients, and in 40% of the current series, a result, we suspect, of greater awareness of this feature. This typically involves a heightened emotional reactivity to poignant but relatively minor triggers, such as a story or tune on radio or TV, or a social encounter, often leading to unexpected tearfulness.

5.4.3.6 INTERICTAL MEMORY DISTURBANCE

Figure 8 indicates potential mechanisms for ALF and AbA. For ALF, '*1*' refers to the possibility that a focal pathology or disturbance in function of limbic structures, most likely the hippocampus, disrupts memory acquisition and/or consolidation. The pathology could be integral to the underlying cause of the epilepsy, a structural result of the epilepsy or reflect an adaptation to the epilepsy: taking our observation that an intrathecal-administered GABA receptor B agonist, Baclofen, can cause ALF (Zeman et al., 2016), together with evidence that experimental epilepsy can induce compensatory inhibitory mechanisms (Palop et al., 2007), we hypothesise that excessive inhibition within the medial temporal lobe (MTL) memory system may be a mechanism of ALF (Schmitz et al., 2017). Secondly ('*2*'), disruption of the normal dialogue between the MTL and the neocortex, required for the consolidation of recently acquired memories could play a role (Baker and Zeman, 2017). Finally ('*3*') – and not to the exclusion of *1* and/or *2* – ictal and interictal discharges may disrupt memory processing.

In the case of AbA, structural pathology ('1') in the MTL, perhaps detectable using high field MRI imaging (Comper et al., 2017, Palombo et al., 2018), could underlie the depletion of autobiographical memories that occurs in TEA, in keeping with the 'multiple (hippocampal) trace' model of remote memory (Moscovitch et al., 2005). Ictal or interictal discharges may delete ('2') or render inaccessible ('3') engrams in the MTL ('1') or neocortex ('4').

5.4.3.7 PROGNOSIS

We have recently reported 10 and 20 year outcomes in patients with TEA followed from the mid-1990s (Zeman et al., 1998) and early 2000s (Butler et al., 2007, Savage et al., 2016, Savage et al., 2019a). TEA does not reduce life expectancy or increase the risk of dementia (Savage et al., 2016). The neuropsychological prognosis is broadly benign, with well-preserved cognitive function in most domains, alongside evidence of moderate decline in memory function over time on standard measures in some (Savage et al., 2016, Savage et al., 2019a). Accelerated long-term forgetting resolved in some individuals over 10 years of follow-up, but persisted at a group level (Savage et al., 2019a). AbA

persisted, with evidence of some improvement in memory for events for the most recent decade (Savage et al., 2019a).

5.5 CONCLUSION

The growing world literature on TEA included 94 cases at the time of our previous review in 2008, among them 50 from our first series; in the current paper we report a further 65 patients studied at our centre and 114 cases from elsewhere reported since 2008. This now substantial patient cohort indicates that TEA is a distinctive form of late-onset limbic epilepsy. It gives rise to recurrent episodes of transient amnesia, typically lasting for around 30 minutes, often on waking, frequently occurring at intervals of around one month. Olfactory hallucinations are a common accompaniment and useful diagnostic clue. There is, in several series, an unexplained male predominance. Interictal memory impairment, specifically ALF and AbA occur in the majority of patients, sometimes associated with a distinctive form of emotional lability. The condition is most often idiopathic, and such cases have a benign prognosis. TEA occasionally occurs as a result of structural pathology and as a manifestation of auto-immune epilepsy. The aetiology of idiopathic cases, the monthly occurrence of seizures in some patients and the mechanisms and interrelationships of the interictal features – amnestic and affective – all warrant further study. The current report establishes TEA as an important, treatable cause of memory loss in older people, often mistaken for dementia, cerebrovascular disease and functional amnesia.

Declaration:

This chapter is soon to be submitted for publication as:

Baker. J., Savage. S., Milton. F., Butler C., Kapur N., Hodges. J. & Zeman A. The Syndrome of Transient Epileptic Amnesia: A combined cohort of 115 patients and literature review.

My contribution to this chapter has been in production of the manuscript (introduction, methods, and results) and literature review. Description of the neuropsychological tests performed and their analysis was provided by SS. The discussion was written by AZ. All named authors will have reviewed and commented on this paper prior to its submission

CHAPTER SIX: ACCELERATED LONG-TERM FORGETTING IN EPILEPSY - AND BEYOND

6.1 INTRODUCTION

Epilepsy can be associated with a variety of cognitive symptoms and impairments. Over the last decade a particular pattern of epilepsy-associated memory impairment has attracted increasing attention. Accelerated Long-term Forgetting (ALF) is the abnormally rapid forgetting of memories over intervals longer than the 30 minutes or so traditionally used to measure 'delayed recall' during a neuropsychological assessment. People with ALF often report that memories 'leak away' more quickly than would be expected, and some studies have reported a correlation between subjective complaints of memory impairment and objective measures of ALF. In this chapter, through a narrative review of the available literature, I review the evolution of this concept, clarifying its clinical presentation and associations, underlying pathophysiology, and treatment options. I review recent evidence that ALF may not be confined to patients with epilepsy

6.2 METHODS

To inform this narrative review of the topic of ALF, I undertook a literature search using PUBMED to identify all relevant articles. A search using the terms 'accelerated AND forgetting' yielded 114 results. Of these, 44 were published in the last 5 years and 64 in the last 10 years. This provides a sense of the relatively recent development of this term and its proliferation over the last decade (Figure 6.1). Papers were excluded when English language texts were not available, where the cases described had already been reported elsewhere or where no formal neuropsychological testing had been performed. The results of the 40 case studies / case series, and 5 review papers on the topic of accelerated forgetting are summarised in table 6.1

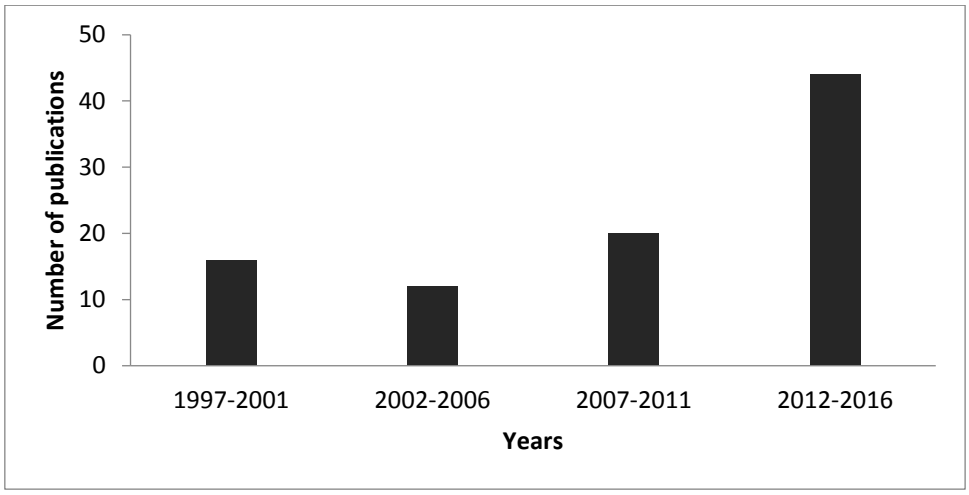


Figure 6.1. Number of publications on ALF 1996-2016

6.3 RESULTS

6.3.1. DEFINING ALF

It has long been recognised that TLE is often associated with memory impairment, but it has generally been assumed that standard testing intervals of half an hour or so are adequate to assess long term retention and forgetting rates. The possibility that accelerated forgetting might become apparent in some patients over intervals longer than those usually studied was first raised by a series of case reports (O'Connor et al., 1997, Kapur et al., 1997, Lucchelli and Spinnler, 1998, Mayes et al., 2003, Cronel-Ohayon et al., 2006).

Author	Year	number of patients	Age (mean)	diagnosis	Test intervals
Giovagnoli	1995	24	38	TLE	1h,24h, 3d,6d,13d
Kapur	1997	1	62	Complex partial seizures	30m, 6w
O'Connor	1997	1	42	Complex partial seizures	2h, 24h, 48h, 72h, 1w
Lucchelli	1998	1	65	Complex partial seizures	10m, 60m, 24h, 1w, 41d
Blake	2000	21	34	TLE	30m, 8w
Mayes	2003	1	46	Complex partial seizures	30m, 3w
Bell	2005	42	37	TLE	30m, 24h
Jokeit	2005	162	38	epilepsy	30m
Manes	2005	7	57	TEA	30m, 6w
Bell	2006	25	39	TLE	30m, 2w
Cronel-Ohayon	2006	1	18	Complex partial seizures	60m, 1w, 29d

Mameniskiene	2006	70	33	TLE	30m, 4w
Butler	2007	24	68	TEA	30m, 1w, 3w
Davidson	2007	21	12	IGE	30m, 1w
Manes	2008	10	64	subjective memory complaints	30m, 6w
Jansari	2010	1	63	TLE	30m, 24h, 1w, 2w, 4w
Muhlert	2010	11	69	TEA	40s, 30m 24h, 1w, 3w
Deak	2011	7	44	TLE	30m, 12h
Galassi	2011	1	58	TLE	30m, 1w
Tramoni	2011	5	43	TLE	1h, 6w
Barkas	2012	12		TLE	3w to 6w
Butler	2012	22	66	TEA	30m, 1w
Narayanan	2012	14	34	TLE	30m, 4w
Wilkinson	2012	27	37	TLE	1h, 6w
Fitzgerald	2013	39		epilepsy	30m, 24h, 4d
Hoefeijzers	2013	17	66	TEA	30m, 1w, 3w
Mary	2013	32		healthy adults - sleep	30m, 1w
McGibbon	2013	1	68	TLE	5m, 30m, 55m, 4h, 24h
Atherton	2014	11	68	TEA	30m, 12h
Evans	2014	7	40	TLE	30m, 1w
Gascoigne	2014	23	13	TLE	30m, 1w
Hoefeijzers	2014	11	59	TEA	30m, 3h, 8h, 24h,1w
Tu	2014	7	51	Thalamic stroke	1h, 24h, 1w, 2w, 4w
Walsh	2014	15	75	MCI	30m, 1w
Landowsky	2015	42	43	25 with head injury	30m, 4h
Miller	2015	7	45	Epilepsy	30m, 1w
Witt	2015	1	35	anti-GAD encephalitis	30m, 1w
Cassel	2016	18	39	TLE	10m, 1d, 1w
Zeman	2016	1	52	Spinal injury/baclofen infusion	30m, 1w
Weston	2016	21	38	AD mutation carriers	30m, 1w
Bell	2007	Review			
Butler	2008	Review			
Zeman	2013	Review			
Elliott	2014	Review			
Geurts	2015	Review			

Table 6.1: summary of ALF studies

Subsequent publications have focused on group studies, predominantly in patients with temporal lobe epilepsy (TLE) (see Table 6.1). Whereas the early case reports involved patients with epilepsy secondary to a previous brain injury, the majority of the group studies have reported ALF in patients with no visible abnormality on MRI scan, in common with the majority of patients with TLE (Manes et al., 2005, Butler et al., 2007) . A number of these single case reports and case series have been summarised previously (Bell and Giovagnoli, 2007, Butler and Zeman, 2008b, Zeman et al., 2013, Elliott et al., 2014).

Patients with TLE show a range of memory impairments, and not all of them will exhibit ALF. Some will have deficits on standard memory test intervals (Mameniskiene et al., 2006); while others will show no impairment even over longer delays (Giovagnoli et al., 1995, Bell et al., 2005, Bell, 2006). However, a number of studies have found evidence of normal or relatively normal memory retention after a 30 minute delay (Blake et al., 2000, Butler et al., 2007) in association with accelerated forgetting after that interval.

ALF is particularly common in association with TEA, a subtype of TLE (Table 6.2). Patients with TEA typically report three distinct forms of memory impairment: amnestic seizures, retrograde memory impairment (the inability to evoke autobiographical memories from the past, often combined with impairment of remote topographical memory), and ALF (Zeman et al., 2013). 44% of patients with TEA report symptoms suggestive of accelerated forgetting (Butler et al., 2007). Moreover, Butler et al reported a correlation between subjective memory complaints and measures of accelerated forgetting, but not with measures of memory obtained at standard intervals (Butler et al., 2009).

If it is accepted that some patients with epilepsy perform normally on memory tests at standard intervals, but show impairment at extended ones, what kinds of learning and memory are affected? The phenomenon has been described in the context of declarative rather than non-declarative or procedural memory (Muhlert et al., 2010), and may especially affect the recall of context-rich episodic memories (Jansari et al., 2010, Tramoni et al., 2011). In the following section I consider the optimal methodology for the assessment of ALF.

Definition of TEA (Butler and Zeman, 2008b)
(1) a history of recurrent witnessed episodes of transient amnesia
(2) cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
(3) evidence for a diagnosis of epilepsy based on one or more of the following:
(a) epileptiform abnormalities on electroencephalography
(b) the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
(c) a clear-cut response to anticonvulsant therapy

Table 6.2: TEA diagnostic criteria (from Butler and Zeman, 2008)

6.3.2 MEASURING ALF

A careful recent review of the literature by Elliott et al., (2014) concluded that ALF is a distinctive and robust clinical phenomenon but also identified a range of methodological variations in previous studies which sometimes hampers the interpretation of results (Elliott et al., 2014). The sources of variation included:

i) **Selection of control participants:** studies have varied in the care with which control participants have been matched to patients on measures of general cognitive functioning, such as IQ, educational background and age. These may all be relevant to long term memory retention and forgetting.

ii) **Test material and procedures**:

a) verbal vs visual material: most but not all studies have compared the learning and forgetting of verbal and visual material: this is desirable, in case there are material specific effects.

b) assessment procedure: most but not all studies have used measures of recall and recognition: this, again, is desirable given evidence that these measures may tap into partially separable processes (Aggleton and Brown, 1999). Elliott et al. review evidence that subtle differences in procedures can affect test results;

c) ceiling and floor effects: these have been present in some studies, limiting their ability to detect and/or compare forgetting in patients and/or controls.

d) matching initial learning: some but not all studies have succeeded in matching initial learning. Where this is not achieved, the interpretation of forgetting curves, from different points of departure, is controversial. Elliott et al discuss a range of techniques used to match initial learning.

e) rehearsal effects: there is a risk, in studies of long-term retention, that participants may rehearse the material they have learned consciously. Differential rehearsal across groups could confound the intended comparison. It is not clear that this is a serious practical problem, but some researchers have used material that would be difficult to rehearse to overcome this obstacle.

f) Short Term Memory (STM) influence: some but not all studies have included a distraction procedure before the measure of immediate recall to obtain a result that is not contaminated by working memory.

iii) **Analysing of forgetting rates**: As mentioned above, where levels of initial learning differ the comparison of forgetting curves is problematic and there is a variety of potential approaches to data analysis.

To minimise these discrepancies, this paper concludes with a series of considerations which it suggests should be applied to future studies in this area (table 6.3).

There is a need to develop a reliable approach to the clinical identification of ALF. Miller et al., (2015) recently assessed 60 healthy control subjects using three standardised measures of memory (Rey Auditory Verbal Learning (RAVLT), Logical Memory (LM), and Aggie Figures) with recall delays of 30 min and 7 days in order to establish normative values (Miller et al., 2015). 15 patients with focal epilepsy were studied using the same tasks. Seven of the patients showed ALF. Although this is a small study the suggestion is that this triad of tests, with a recall period of 7 days, may be an effective means of identifying ALF in patients with epilepsy who complain of memory impairment.

Methodological Guidance for Further Studies in ALF (Elliott et al., 2014)
1. Patient and control groups should be matched, at least for age and intellectual ability.
2. Ideally, both verbal and non-verbal test material should be used.
3. Ideally, forgetting should be measured using both recall and recognition tests.
4. Ceiling and floor effects should be avoided as far as possible.
5. The potential for rehearsal and repeated recall should be avoided as far as possible.
6. The immediate delay period should be long enough to ensure information is stored in Long Term Memory (LTM) and retrieval is not reliant on STM processes.
7. Effort should be made to equate initial learning (whilst avoiding overlearning).

Table 6.3: methodological guidance for ALF studies (From Elliott et al., 2014)

6.3.3. THE FORGETTING INTERVAL IN ALF

The formation of memories is a highly complex, time-demanding process involving a series of biological steps and anatomical regions (figure 6.2). Disruption of any of these steps can impair memory (Kopelman, 2002). Initial memory acquisition requires that information gains access to the relevant memory system ('encoding') with rapid associated changes in synaptic strength ('early' consolidation) Over time, the fragile early memory trace is strengthened ('late consolidation'), at least in part through processes of 'replay'. Memories must then be stored, and retrieved when required. There is evidence that they remain labile during storage, especially at times of retrieval, when they may be strengthened or weakened by a process of 'reconsolidation'. The complexity of these processes challenges the simple, traditional distinction in cognitive psychology between 'short' and 'long term' memory, and predicts the existence of forms of amnesia corresponding to disruption of these processes. The locus of the memory process disturbed in ALF remains unclear but studies of its time course are relevant to determining this: if ALF is, in fact, predictable from the point of memory acquisition then it may well be due to pathology of encoding or early acquisition. If, however, at least in some instances, ALF only becomes apparent sometime after acquisition, then later processes of consolidation may be involved, though, as I mention below, behavioural evidence alone may never be sufficient to establish this firmly.

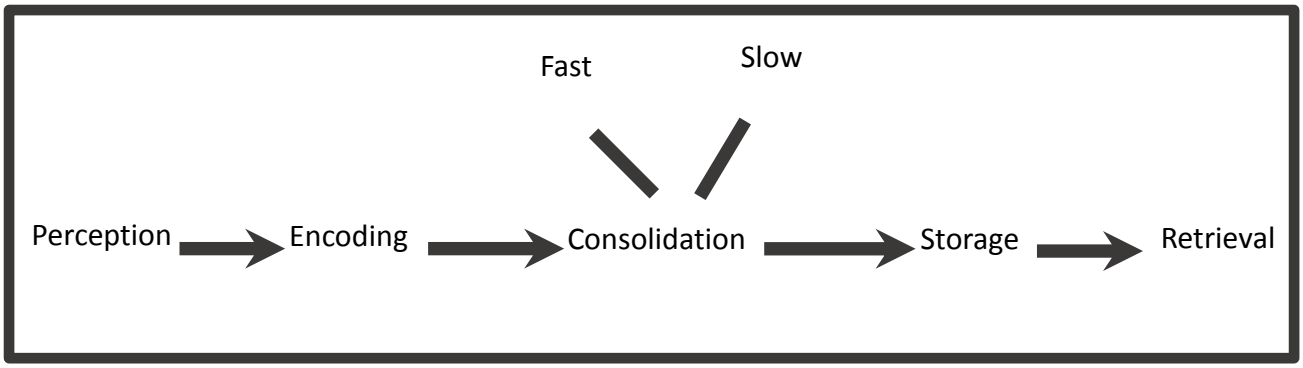


Figure 6.2. Representation of multiple stages in memory process

A variety of different delays has been investigated, from several hours to several weeks (see Table 1)

The onset of ALF over shorter delays has been examined by (Hoefeijzers et al., 2015). This study investigates the recall of word lists in TEA patients and controls at intervals of 30 minutes, 3 hours, 8 hours and 24 hours. Although the TEA patients were not significantly different from controls at the immediate and 30 minute intervals, there were significant differences between 30 minutes and 8 hours. There was a reduction in recall between 30 minutes and 3 hours but this did not reach significance. No further forgetting was observed over the first night in either group (i.e., between 8 hours and 24 hours).

Other studies have identified evidence of ALF just one hour after acquisition (Wilkinson et al., 2012, McGibbon and Jansari, 2013). Wilkinson et al., (2012) reports accelerated forgetting of both verbal and non-verbal material in a cohort of 27 TLE patients. However, the pattern of forgetting was dependent on the different materials learnt and on the lateralisation of hippocampal sclerosis. Those with left sided abnormalities demonstrated accelerated forgetting of verbal material at the 1-hour delay, whereas the right-sided group showed normal retention at this interval with accelerated forgetting over a 6-week delay. In contrast, patients with right-sided hippocampal sclerosis showed faster forgetting over 1-hour of the non-verbal task when compared to those with left sided abnormalities (Wilkinson et al., 2012).

The time course of forgetting has recently been examined in detail by Cassel (2016). In this paper, to clarify the interval after learning at which ALF can be

said to start, 14 TLE patients were examined using a story and a route learning task. Recall was tested at intervals of 30 seconds (following a distractor task), 10 minutes, one day and one week. It was found that patients' and controls' performance did not differ at 30 seconds on either task (Cassel et al., 2016). However, TLE patients required more learning trials to reach criterion. In the story task, accelerated forgetting was progressive from 30 seconds onwards, although differences in forgetting rate only became statistically significant after one week. In the route learning task, patients showed faster forgetting over the first 10 minutes with comparable forgetting rates thereafter. These data suggest that in this group of patients accelerated forgetting occurs as a consequence of impaired acquisition/early consolidation.

In contrast to these findings, in a reanalysis of data from the study of Butler et al (2007), Hoefeijzers et al. (2015) examined the fate of words which had received the same number of learning trials and retrievals in patients with TEA and control participants in a world list learning study. There was no significant difference between the two groups on an initial recall test at 30 minutes. However, recall performance was significantly lower for TEA patients when compared to controls after 1 week, suggesting a disruption of 'late' consolidation.

As an aside, I note three relevant complexities: first, it may well be that earlier and later processes interact in such a way that an early defect is amplified by its effects at later stages: for example, recurrent rounds of 'replay' may give rise to a widening difference between memories differing slightly in strength at or soon after acquisition (Zeman et al., 2016). Second, it is not clear that purely behavioural data will ever be sufficient to resolve the question of the locus of the underlying impairment in ALF, as I currently have no absolutely reliable behavioural measure of memory strength: it is likely, therefore, that settling this question will require direct measures of brain activity associated with the various stages of memory processing. Third, patients describe the loss of memories over varied time-scales, from days to months: it may be that different mechanisms underlie ALF in different clinical situations.

6.3.4. ALF AND SLEEP

Theories of memory consolidation have placed particular emphasis on the role of sleep in the long-term retention of declarative memories. Given the possibility that ALF may be a disorder of memory consolidation, its connection with sleep has been investigated. In a study of sleep quality and in particular its association to ALF, Mary et al., (2013) found that increased sleep fragmentation ('intra-sleep awakenings') was associated with ALF (Mary et al., 2013). However, this study also suggests that this sleep fragmentation was not enough by itself to explain the phenomenon and that therefore memory consolidation processes cannot depend exclusively on sleep quality after learning. In support of this a number of studies have shown that ALF can occur without an intervening period of sleep.

The frequent occurrence of amnesic attacks on awakening in patients with TEA (Butler et al., 2007), raised a suspicion that ALF in this condition might be related to disruption of sleep-related memory processing. However, Atherton et al., (2014) found ALF patients derived the same benefit from sleep as controls. In this study, TEA patients, tested after an 8 hour interval, showed ALF after a day awake but not following a comparable period of overnight sleep (Atherton et al., 2014). This suggests that ALF in TEA may be related more to the effects of retroactive interference from novel information than to a disruption of sleep-related consolidation. This view is supported by other studies examining TEA and TLE which have also shown ALF during waking hours which is not worsened by an intervening period of sleep (Deak et al., 2011, Fitzgerald et al., 2013, Hoefeijzers et al., 2015).

6.3.5. ALF IN CHILDREN WITH EPILEPSY

A number of studies have attempted to identify ALF in children with epilepsy (Cronel-Ohayon et al., 2006, Davidson et al., 2007, Gascoigne et al., 2014). Assessing ALF in children is not straightforward. However, given the long term implications of an accelerated rate of forgetting for young people in full-time education, it is certainly clinically important. Although temporal lobe epilepsy is the most common form of adult-onset epilepsy, seizures involving the temporal lobes are also common in children. Gascoigne et al., (2014) identify twenty-three children between the ages of 6 and 16 years of age with temporal lobe epilepsy.

7 of these patients had had a temporal lobe resection (Gascoigne et al., 2014). ALF was identified in this group for verbal, but not visual information. No correlation was identified between epilepsy severity and ALF. ALF has also been observed in children with generalised epilepsy (Davidson et al., 2007).

6.3.6. TREATMENT OF ALF IN EPILEPSY

Several studies have investigated the response to treatments ranging from repeated prompting (McGibbon and Jansari, 2013) and medication (Midorikawa and Kawamura, 2007, Razavi et al., 2010, Barkas et al., 2012) to surgery (Gallassi et al., 2011, Evans et al., 2014).

At the more conservative end of this spectrum, McGibbon and Jansari, (2013) examined the role of repeated recall in reducing the effects of ALF (McGibbon and Jansari, 2013). They found that repeated recall has a protective effect against the delayed forgetting seen in ALF. Tramoni et al (2011) reported normal performance over 6 weeks in a task in which facts were taught initially to a criterion of 90% correct in patients who showed ALF for episodic information (Tramoni et al., 2011). Further work examining the value and limits of such strategies in patients with ALF would be valuable

If ALF is a manifestation of ongoing epileptic activity it is reasonable to suppose that anticonvulsant medications may have a role in reducing these memory symptoms. Midorikawa and Kawamura (2007) showed improvement of ALF but not retrograde amnesia in a patient with TEA following the initiation of anticonvulsant medication (Midorikawa and Kawamura, 2007). Razavi et al., (2010) also found resolution of memory symptoms in their TEA patient following the introduction of carbamazepine (Razavi et al., 2010). However Jansari et al., (2010) did not find a significant improvement in the rate of long-term forgetting in their patient after lamotrigine had been started (Jansari et al., 2010).

In cases of medically intractable temporal lobe epilepsy, surgery remains the best option for seizure control. A number of studies have looked at the role of temporal lobectomy in relation to ALF. Results have been mixed. In their case report Galassi et al. (2011) show that a left temporal polectomy reduced seizure frequency and ALF in a 58yr old male patient with a 20 year history of medically intractable epilepsy (Gallassi et al., 2011). Evans et al (2014) report a cohort of

seven patients with temporal lobe epilepsy (Evans et al., 2014). A longitudinal design was used to assess ALF pre- and post-epilepsy surgery. Visual and verbal materials were used with recall and recognition tests. ALF was confirmed prior to surgery. The study identified a degree of impairment of initial learning in the group post-surgery, in keeping with hippocampal resection, which complicated the interpretation of further forgetting. However, retention was unimpaired between the 30 minute and one week delays in all 8 subtests following surgery. It is also worth noting that at the time of testing in these patients, none had had a change in their epilepsy medication, precluding this from being a contributing factor in their improvement. Given that the indication for surgery in these patients was medically intractable epilepsy, the study concludes that persistent and recurrent seizure activity may have had a causative role in the pattern of forgetting before surgery.

Some novel therapeutic approaches have also been investigated. This includes the use of the selective serotonin reuptake inhibitor fluoxetine (Barkas et al., 2012). In this paper it was shown that patients with hippocampal sclerosis show impairments of acquisition for a spatial task with accelerated forgetting of this task once learned. Administration of fluoxetine reversed the learning deficit, but left the pattern of accelerated forgetting unchanged.

6.3.7. ALF IN OTHER CONDITIONS

While ALF has been described predominantly in epilepsy, a growing literature is exploring the possibility that it can occur in other contexts. I highlight recent papers describing ALF in cases with limbic encephalitis, stroke, subjective memory complaints, mild cognitive impairment (MCI) and Alzheimer's disease (Manes et al., 2008, Walsh et al., 2014, Weston et al., 2018) and during intrathecal therapy with the GABA (B) receptor agonist, Baclofen.

In recent years a growing variety of types of autoimmune limbic encephalitis have been described, typically presenting with memory disturbance, seizures, emotional symptoms and personality change. Witt et al., (2015) describes a case of ALF associated with glutamic acid decarboxylase (GAD) antibody related limbic encephalitis (Witt et al., 2015). This patient, a 35-year-old male, complained of severe anterograde and retrograde memory deficits characterized

by accelerated long-term forgetting. Video EEG monitoring confirmed a left temporal epileptic focus and subclinical seizure activity but no overt seizures at the time of initial presentation. Cognitive testing identified normal learning and initial recall at 30 minutes but significantly impaired recall for information at 1 week, in keeping with the pattern seen in other ALF patients. He was treated with monthly steroid pulses and anticonvulsant treatment and reported an improvement in his anterograde memory.

ALF has also been demonstrated in patients with thalamic stroke (Tu et al., 2014). In this study, using a visual task, 7 patients with previous thalamic strokes were tested at intervals of: 1 h, 24 h, 1 week, 2 weeks, and 4 weeks. Accelerated forgetting of newly acquired contextual information was identified in patients within 24 h when compared to healthy controls.

It is not surprising, given the clinical features and demographics of reported cases of ALF, that there has been interest in its potential relationship to MCI, particularly as ALF has been shown to correspond well to subjective memory concerns. Manes et al., (2005) in a relatively early paper on the topic of ALF showed that accelerated forgetting was identifiable in patients attending a memory clinic with subjective memory concerns who performed normally in standard neuropsychological tests (Manes et al., 2005). In this study of 10 individuals with complaints of memory loss but normal cognitive evaluation, 7 patients with MCI and 9 healthy controls, recall of both verbal and non-verbal information was tested immediately and then subsequently at intervals of 3 minutes and 6 weeks. There was no significant difference between the control group and the group with memory complaints on logical memory or the Rey complex figure at the immediate and 30 minute intervals, but a significant difference had developed by 6 weeks. At this time point the scores of the cognitively normal with memory complaints group approached those of the MCI group, with no significant difference between them. The relationship between MCI and ALF has since been explored further by Walsh et al., (2015). In this study, although MCI subjects had an increased rate of forgetting within the first 30-minutes, a greater rate of forgetting was also identified between the 30-minute and 1-week recall sessions (Walsh et al., 2014). This result is important as it shows that the standard tests performed in the memory clinic, which typically involve a delay of 30 minutes, may under-estimate the deficits experienced by this MCI cohort.

In a very recent study Weston investigated whether ALF may be an early feature of Alzheimer's disease (Weston et al., 2018). In a study of 21 carriers of pathological, AD-causing mutations and 11 control patients, matched for age and performance on standard memory tests, accelerated long-term forgetting for both verbal and non-verbal material was found in the mutation carriers at 7 days. These pre-symptomatic AD patients were tested on average 7.2 years before their predicted symptom onset. Patients and controls showed similar performance at an initial recall interval of 30 minutes. It is therefore suggested that ALF may be an early, pre-symptomatic feature of familial Alzheimer's disease, indeed perhaps the earliest feature of AD-related cognitive decline.

A recent review by Geurts et al (2015), while highlighting the possible occurrence of ALF in early AD, as just discussed, noted a lack of evidence for ALF in 8/11 studies ranging over Korsakoff's syndrome, depression (with or without ECT), traumatic brain injury and multiple sclerosis (Geurts et al., 2015).

Finally, ALF has also been described as side effect of medication. Baclofen is a GABA (B) receptor agonist. It is used widely for conditions causing increased muscle tone and spasticity, particularly when associated with pain. In a recent paper ALF was identified in a patient receiving treatment with an intrathecal baclofen pump (Zeman et al., 2016). During a period of dose escalation, the patient reported a constellation of memory disorders very similar to those seen in TEA: amnestic episodes, ALF and autobiographical amnesia. These were confirmed on objective testing. As the baclofen dose was reduced the amnestic episodes and ALF resolved while the autobiographical amnesia persisted. While it is possible that baclofen therapy, given at unusually high doses in this case, induced TEA, the authors also raise the possibility that signalling at the GABA (B) receptor may play a specific role in ALF.

6.3.8. PATHOPHYSIOLOGY OF ALF

Given that ALF appears to be a distinctive clinical phenomenon, two key questions about its nature come to the fore: first, is it a disorder of memory acquisition and early consolidation or of later phases of consolidation? This has already been discussed above, in section 6.3.3. Second, is it a consequence of

disturbed physiology, disordered anatomy or some additional factors such as mood or drug treatment (table 6.4).

In the context of epilepsy, might ALF be a direct consequence of seizures? They do not appear to be *required* for ALF as ALF has been demonstrated in their absence, for example in patients with TEA (see e.g. Butler et al, 2007) and some authors, for example Blake et al. (2000), found no relationship between overt seizure frequency and memory performance (Blake et al., 2000). However, Mameniskiene et al. (2006) reported a positive correlation between long-term forgetting and seizures during their experimental period. They also identified a relationship between *subclinical* epileptiform EEG activity and long-term forgetting (Mameniskiene et al., 2006). This relationship was confirmed by Fitzgerald et al., (2013) who report evidence that inter-ictal discharges disrupt memory consolidation (Fitzgerald et al., 2013). The reduction of ALF by treatment in at least some patients also points to a role for disordered physiology in its causation.

Possible Mechanisms for ALF in Epileptic Patients
1. Clinical or subclinical seizure activity
2. Structural brain pathology
3. Side effect of anti-convulsant therapy
4. Psychological mechanisms

Table 6.4: possible mechanisms for ALF in epileptic patients

Material-specific differences in learning rates could potentially arise from variations in the locations of an epileptogenic focus, and the origin of the epileptic activity. However, previous data have not consistently shown that hemispheric differences cause material-specificity in ALF. Blake et al. (2000) using a test of verbal memory, identified ALF in patients with TLE originating from the left but not the right hemisphere (Blake et al., 2000). However, in an earlier investigation, Martin et al. (1991) were not able to find a hemispheric effect when testing verbal memory. Other studies have also shown ALF for both verbal and non-verbal

information regardless of the site of activity (Mameniskiene et al., 2006, Butler et al., 2007).

There is, therefore, some tentative evidence that disordered physiology contributes to ALF in at least some patients. Does disturbed anatomy also play a role? Several of the early case studies documented ALF in patients with focal pathology. Subsequent group studies have identified abnormalities within and beyond the hippocampus in patients with Transient Epileptic Amnesia (Butler et al., 2007, Butler and Zeman, 2008a, Mosbah et al., 2014). Tramoni et al., 2011 identified metabolic changes in the temporal lobes using PET and magnetic resonance spectroscopy in patients with temporal lobe epilepsy and ALF (Tramoni et al., 2011). The occurrence of ALF in patients with preclinical AD and MCI which ultimately give rise to structural pathology in the temporal lobes may also point to a role for structural pathology. However, this evidence is equivocal as anatomical and physiological disturbance go hand in hand in AD (Vossel et al., 2013), and, in general, attempts to correlate the degree of structural change with the extent of ALF have been unsuccessful. Thus the role of structural pathology in ALF remains uncertain.

It has also been suggested that the pattern of memory impairment seen in ALF among patients with epilepsy could be a consequence of anticonvulsant medication. This seems unlikely, given that patients often report ALF prior to the initiation of anticonvulsant therapies and, as we have seen, often report an improvement in memory following the introduction of medications to reduce seizure frequency (Gallassi et al., 2011, Butler et al., 2007). However, there is certainly some evidence that antiepileptic drugs can negatively affect cognition (Ortinski and Meador, 2004, Jokeit et al., 2005). These negative effects of anticonvulsant medications are most commonly seen with higher doses and the use of polypharmacy. Jokeit et al., (2005) investigated this question (Jokeit et al., 2005). It was shown that high serum levels of carbamazepine, phenobarbital or phenytoin in patients with refractory temporal lobe epilepsy were associated with impaired performance in verbal and nonverbal memory retention tasks when compared to patients with lower levels. However, neither high anticonvulsant doses nor the use of multiple medications are common among patients with epilepsy and ALF. TEA patients, in particular, are typically responsive to low doses of a single epilepsy medication (Butler and Zeman, 2008b). Moreover, it is

rare for patients with ALF to be treated with the older anti-convulsants, which are more prone to cognitive side-effects.

Historically, discrepancies between subjective reports of memory impairment and normal performance on neuropsychological testing have often been attributed to low mood or poor self-esteem (Giovagnoli et al., 1995, Elixhauser et al., 1999). The development of reliable paradigms for identifying and diagnosing ALF has shown that mood is unlikely to play a major causal role in this condition. Several studies have reported an absence of correlation between ratings of mood and ALF (Blake et al., 2000, Mameniskiene et al., 2006, Butler et al., 2007). If ALF were a manifestation of low mood per se we would expect to see an accelerated rate of forgetting in patients with depression: this has not been shown on previous studies (Lewis and Kopelman, 1998).

6.4 CONCLUSION

Since early case reports documented a form of long-term forgetting which occurred at delays longer than those utilised as part of standard memory testing, the literature on accelerated long-term forgetting has grown substantially. There is now a significant body of evidence that ALF occurs as a clinical phenomenon, especially in the context of epilepsy. There is also growing evidence that this pattern of forgetting occurs in conditions other than temporal lobe epilepsy, although this remains the most common cause. Recent studies of ALF in amnestic MCI and pre-symptomatic Alzheimer's disease patients will no doubt stimulate further interest in the topic.

A range of important questions about ALF await a definitive answer. There is continuing disagreement and uncertainty about whether ALF results from a deficit of memory acquisition/early consolidation or of later phases of consolidation. Similarly, the roles of physiological and structural disturbance in causing ALF remain uncertain. These various possibilities are not mutually exclusive: It may well be that early and late consolidation, physiological and structural pathologies are all involved, to varying degrees across differing clinical contexts. Finally, further work is required to develop reliable methods for eliciting ALF in everyday practice.

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My contribution to this chapter was in performing the literature review and writing the manuscript, which was reviewed and amended by AZ prior to submission

CHAPTER SEVEN: DIFFERENTIATING TRANSIENT EPILEPTIC AMNESIA FROM MILD COGNITIVE IMPAIRMENT AND EPILEPSY IN DEMENTIA

7.1 INTRODUCTION

Patients with TEA experience epileptic seizures characterised primarily by a transient impairment of memory. These seizures sometimes include brief periods of unresponsiveness and other ictal features, including olfactory hallucinations and motor automatisms. As I have also shown, epileptic seizures occurring in patients with dementia can lead to behavioural arrest and altered responsiveness, as well as periods of increased confusion and amnesia. In previous chapters we have described the variety of memory impairments reported by patients with transient epileptic amnesia (TEA). The accelerated long-term forgetting (ALF) seen in these patients has also been described in patients with Mild Cognitive Impairment (MCI) and in the early stages of Alzheimer's Disease (AD) (Cretin et al., 2014, Del Felice et al., 2014). From this evidence it is clear that these two clinical presentations (TEA, and epilepsy in dementia) have features in common which may lead to diagnostic confusion. In this chapter I aim to compare and contrast these conditions with the objective of developing a decision aid that will help to distinguish them efficiently in typical clinical settings.

Through the design of the PrESIDe study, I also collected neuropsychological data on a proportion of patients (those diagnosed with MCI in the memory clinic) at the time of their baseline PrESIDe assessment, in order to ensure diagnostic accuracy. It was also anticipated that some of these patients would have progressed from MCI to dementia in the intervening period. Many of these same measures were also collected as part of the TIME study. These parallel neuropsychological testing regimes enable us to compare these two groups of patients (TEA, and MCI) in order to further establish what these two conditions may have in common and the ways in which they are different.

7.2 METHODS

7.2.1 PARTICIPANTS

This retrospective study examined the case notes of two groups of patients enrolled in two separate studies. The Impairment of Memory in Epilepsy (TIME) study has established a cohort of 115 patients with TEA. In previous chapters of this thesis I have described the clinical and neuropsychological features of this group. The Presentation of Epileptic Seizures in Dementia (PrESIDe) study assessed 144 patients with MCI or dementia and identified a clinical suspicion of epilepsy in 37 (25.7%). Here I compare the relevant demographic and clinical features in these patients.

The PrESIDe cohort includes 39 patients in whom a memory clinic diagnosis of MCI was made. This diagnosis was reassessed at the time of their initial PrESIDe interview. Using recognised criteria (Albert et al., 2011), the MCI diagnosis was confirmed in 20/39 (51.28%). The remainder were given a diagnosis of Alzheimer's disease at the time of their PrESIDe assessment (McKhann et al., 2011). I am also able to compare these MCI patients to our TEA cohort in order to better differentiate these two conditions (TEA and MCI).

7.2.2 COGNITIVE FUNCTION MEASURES

The Addenbrooke's Cognitive Examination - Version III (ACE-III) scores were compared as a measure of cognitive function. A diagnosis of MCI was reached if a participant performed 1-1.5 standard deviations below age- and education-matched normative data, as per diagnostic guidelines (Albert et al., 2011). Further cognitive tests: The Rey-Osterrieth Complex Figure (RCF) (appendix7), Rey Auditory Verbal Learning Test (RAVLT) (appendix8), Trail Making Test (TMT - versions A and B) (appendix11), and Digit Span (appendix12), were available in a proportion of patients in the PrESIDe group (those in whom a diagnosis of MCI was made at the memory clinic) and in all of the TIME patients. For the RAVLT, the administration was the same as in the TIME study. A list of 15 words was presented orally over a maximum of 10 trials until at least 12 words (80% accuracy) could be recalled within a given learning trial. Upon reaching this criterion, participants were instructed to count backwards out aloud from 100 for 40 seconds, to prevent rehearsal of words and reliance upon working memory to aid recall. Recall of the words was assessed immediately following this distractor task, and once again at a delay of 30 minutes.

7.2.3 ANALYSIS OF SEIZURE FEATURES

In earlier chapters I have described the seizure semiology of these two groups of patients. I have identified the prevalence of several key seizure features in both the TEA and epilepsy in dementia populations: seizures on waking, pure amnestic seizures, generalised tonic-clonic seizures, altered responsiveness, motor automatisms, and olfactory hallucinations. Seizure features were compared in order to elucidate how patients in these two groups, and those closest to them, described these episodes (including the periods preceding and following them) and any persisting interictal deficits.

7.2.4 NEURORADIOLOGICAL FEATURES

CT head scan reports were obtained for all patients in the PrESIDe study. Where these had been performed, MRI scan results were also obtained. In the TIME study, referring clinicians were contacted to request MRI reports for all patients.

7.2.5 ETHICAL APPROVAL

Ethical approval for these two studies was obtained independently and has been described in earlier chapters.

7.2.6 STATISTICAL ANALYSIS

Between-group analysis of demographic features and cognitive test performance was performed using independent sample t-tests. Chi-square testing was performed to compare proportions between participants and controls. Multiple linear regression analysis was performed to assess the relationship between dependent and independent variables. Statistical significance was judged as any p-value <0.05. IBM SPSS statistics 22.0 and STATA were used to perform data analysis.

7.3 RESULTS

7.3.1 DEMOGRAPHIC FEATURES

The 115 TIME patients with TEA and the 37 PrESIDe patients with Epilepsy in MCI or dementia were compared in terms of background demographic features (Age, gender, educational background). These background demographic

features of these cohorts are shown in table 7.1. Whilst in both phases of the TIME study TEA has been shown to be more common in men than women, there was no significant difference in terms of the gender balance between the two cohorts. A significant difference was identified when the two groups were compared in terms of the onset of seizures, and age at diagnosis. The average age of seizure onset in the dementia group was 76.91 years, 15 years older than in the TEA group.

	TEA (n=115)	PrESIDe (M:F) (n=37)	p-value
Gender	85:30	22:15	0.095
age at memory symptom onset		75.59 (51-89)	
age at seizure onset	61.7 (26-77)	76.91 (55-91)	**<0.001**
age at diagnosis	66.7	78.14 (61-92)	**<0.001**

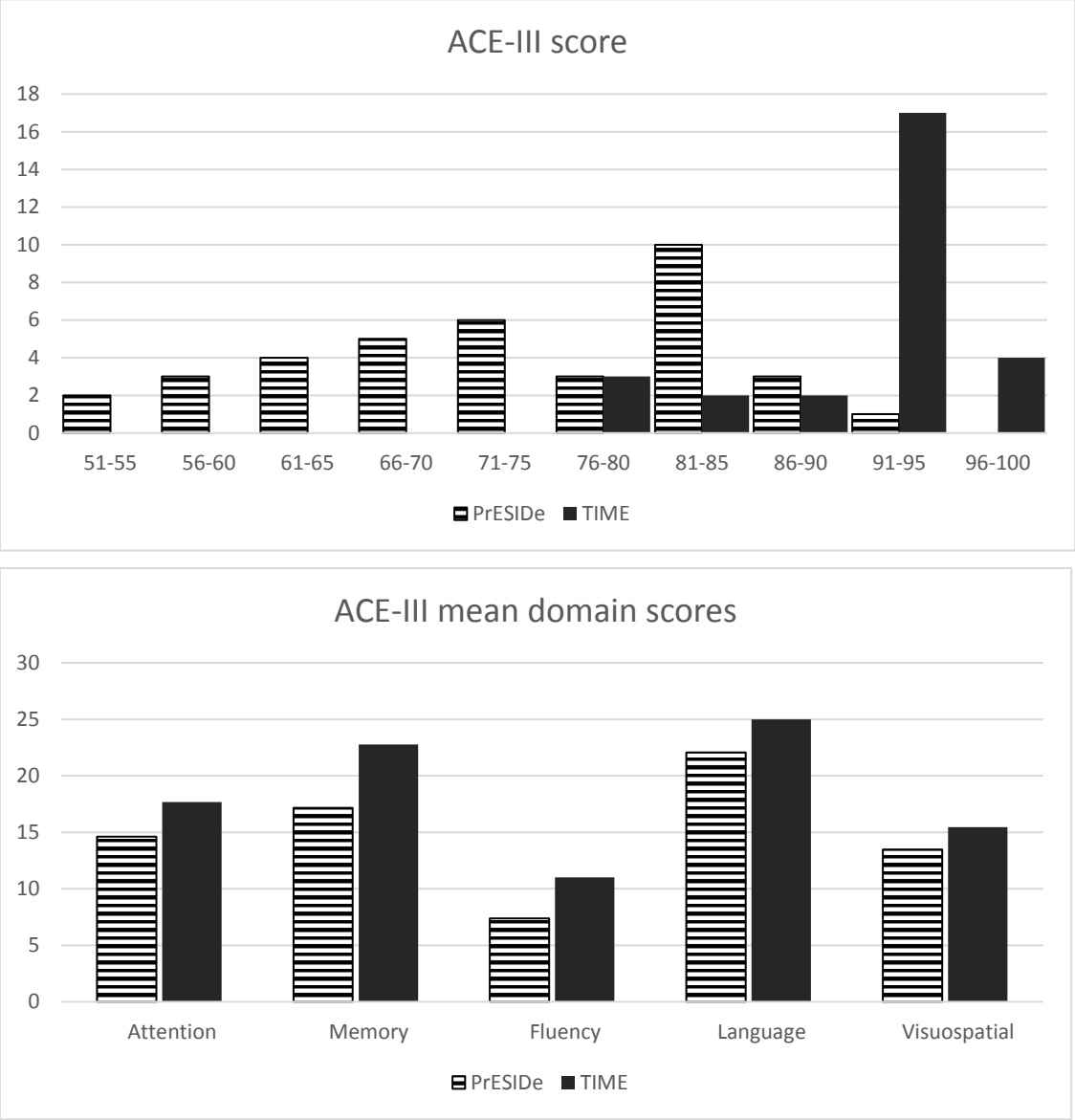
(Table 7.1: comparison of the demographic features in TIME and PrESIDe)

7.3.2 COGNITIVE TEST PERFORMANCE

All patients included in the PrESIDe study underwent cognitive testing using the ACE-III examination. Of the 65 participants in the TIME2 study, ACE-III scoring was available in 28/65, with subdomain scoring available in 13/65. A comparison of the overall ACE-III scores, as well as domain scores in these two groups is shown in table 7.2.

	TEA (n=28)*	PrESIDe (n=37)	p-value	PrESIDe controls (n=80)
ACE-III (mean and SD)	91.21 (5.95)	74.7 (10.37)	**<0.001**	95.24 (2.37)
ACE-III (range)	76-100	53-91		89-99
Total with ACE-III <88	5 (17.86%)	34 (91.89%)	**<0.001**	0 (0%)
Total with ACE-III <82	3 (10.71%)	25 (67.57%)	**<0.001**	
Subdomain:				
Attention	17.69 (0.63)	14.61 (3.01)	**<0.001**	17.7 (0.60)
Memory	22.77 (2.74)	17.15 (4.69)	**<0.001**	24.69 (1.29)
Fluency	11.01 (2.99)	7.39 (2.49)	**<0.001**	11.58 (1.35)
Language	25 (1.41)	22.06 (2.89)	**0.001**	25.76 (0.51)
Visuospatial	15.46 (0.78)	13.48 (2.53)	**0.008**	15.51 (0.78)

(Table 7.2: Comparing the cognitive test performance (ACE-III) of TIME and PrESIDe participants. *subdomain scores available in 13/28 patients with TEA)



(Figure 7.1: comparison of ACE-III total and domain ACE-III between TIME and PrESIDe studies)

Although the number of participants in TIME for whom full subdomain data are available is limited, I have identified significant differences between the two cohorts both in the overall scores and in all cognitive domains probed by this test (Figure 7.1). Conversely no significant differences were identified when the TIME participants were compared to the PrESIDe control participants. Whilst the control participants performed better in each domain on the test, at no point was this difference significant.

7.3.3 NEUROPSYCHOLOGICAL PERFORMANCE (COMPARING TEA, MCI AND AD)

39/144 patients in the PrESIDe cohort were given a diagnosis of MCI at their memory clinic appointment; in 20/39 (51.28%) the diagnosis was confirmed using research criteria at the time of PrESIDe baseline assessment (in the remaining 19/39 (48.7%) the diagnosis was changed to AD. The delay from memory clinic to PrESIDe assessment was 12-52 weeks (median 27). The performance of these groups in comparison to the TEA group is outlined in table 7.3.

On a test of visual memory (RCF) there was no significant difference between the two groups on the initial copy of this figure. However, on the recall of this figure after 30 minutes the MCI group performed significantly better than the AD participants (p=0.033). On the TMT, the two groups were comparable on version A (p=0.143) but again the MCI group performed significantly better on version B (p=0.008). The MCI participants also outperformed the AD participants on the digit span test. Patients with MCI scored significantly better when asked to repeat the digit sequence backwards (p=0.012) and in terms of their total score (correct responses forwards + backwards) (p=0.02). Interpreting the test of verbal memory (RAVLT) was more complicated as several of the AD patients failed to meet the specified learning criteria. However, whether or not the patients who failed to meet the learning criteria were excluded, MCI patients performed significantly better after a brief distraction (counting backwards from 100 for 40 seconds) and a standard delay of 30 minutes.

	Test	TIME2 (n=53)	TEA vs MCI (p-value)	MCI total (n=20)	MCI vs AD (p-value)	AD total (n=19)
RAVLT	trials to criteria	5.46 (2.91)	0.436	6.25 (2.90)	N/A	N/A
	40s (/15)	9.96 (2.08)	**0.003**	7.25 (3.25)	**0.006**	4.65 (2.19)
	30 mins (/15)	8.68 (2.87)	**0.005**	5.42 (3.45)	**0.013**	2.81 (2.55)
RCF	Copy (/36)	31.74 (4.38)	0.614	31.08 (2.31)	0.596	30.02 (6.64)
	30 min recall	15.3 (5.9)	**0.002**	10.67 (3.53)	**0.033**	6.17 (6.59)
TMT	A (secs)	36.60 (13.23)	**0.006**	49.72 (11.79)	0.143	60.39 (23.21)
	B (secs)	93.76 (47.73)	0.345	109.36 (43.32)	**0.008**	169.30 (66.79)
Digit Span	Max forward	6.85 (1.23)	0.651	6.64 (1.21)	0.128	6.05 (0.85)
	Max backward	4.95 (1.47)	0.919	5.00 (0.89)	**0.012**	4.21 (0.71)
	total score	18.20 (3.74)	0.637	17.55 (3.42)	**0.020**	14.84 (2.54)

(Table 7.3: performance in neuropsychological testing)

Patients with TEA performed better on neuropsychological testing than patients with MCI. This performance was significantly better on the RAVLT after the 40s (p=0.003) and 30min (p=0.005) delays. There was no significant difference in the learning trials required to meet criteria. On the RCF the TEA group performed significantly better on the 30-min recall (p=0.002). There was no difference on the initial copy performance (p=0.614). On TMT the TEA patients performed significantly better than the MCI patients on version A, but not version B.

7.3.4 SEIZURE FEATURES

Patients who experience epileptic seizures as part of their dementia were significantly more likely to have seizures where loss of awareness is a feature (Table 7.4). Automatisms occurred in a similar prevalence across both groups, although olfactory hallucinations were significantly more common in the TEA group. More than 50% of participants in both groups experienced amnestic episodes on waking in the morning, although this phenomenon was reported significantly more commonly in patients with TEA.

	TEA (n=115)	PrESIDe (n=37)	p-value
Unresponsiveness	39%	78%	**<0.001**
Automatisms	41%	38%	0.747
Olfactory hallucination	43%	5%	**<0.001**
Seizures on waking	85%	54%	**<0.001**
Amnesia as sole seizure feature	24%	5%	**0.011**
Response to medication	93%	67%*	**0.025**
Seizure frequency (median)	12 (IQR 6-25)	6	
Seizure duration (median, range)	15-30 mins (<1 min to days)	5-10 mins (1 min to 2 hours)	

(Table 7.4: A comparison of seizure features in TIME and PrESIDe, * 6 patients in PrESIDe group were taking an anti-epileptic medication)

7.3.5 NEURORADIOLOGICAL FINDINGS

Standard procedure in the regional memory clinic is for patients to receive a CT brain scan. Reports of these scans were available in 37/37 PrESIDe patients. Atrophy was reported in 29/37 (78.4%). In 14/29 (48.3%) this was felt to be in keeping with / commensurate with the patient's age. In 7/29 (24.1%) in was clear from the report that the atrophy was in excess of the patient's age. In the remaining 8/29 (27.6%) no comment was made as to whether or not the atrophy seen was in keeping with the patient's age. In 24/29 patients the atrophy was reported to be generalised / no lobar predominance. In the remaining 5/29, focal hippocampal / temporal lobe atrophy was reported.

The presence of small vessel ischaemic change was reported in 23/37 patients (62.2%). There were no small vessel ischaemic changes in 6/37 patients. No comment on small vessel ischaemic change was made in the remaining 8 patients. In the 23 patients in whom small vessel disease was reported, this was described as mild, minor or grade 1 in 8/23 (34.8%), and moderate, grade 2 or grade 3 in 10/23 (43.5%). In the remaining 5/23 (21.7%) the degree of SVD was not described.

Focal lesions were reported in 6/37 patients (16.2%). In 5/6 cases this lesion was an established area of ischaemia (Right internal capsule, right frontal lobe, right corona radiata, bilateral basal ganglia, adjacent to temporal horn of right lateral ventricle). In the remaining patient the focal abnormality was a probable neuroglial cyst within the left putamen.

MRI scans had been performed in 4/37 (10.8%) of patients. In 2/4 of these patients (50%) hippocampal atrophy which had not been reported on the CT scan was identified.

MRI scan reports are available in 59/65 (90.8%) patients in the TIME2 study. Small vessel ischaemic changes were reported in 12/65 (18.5%) of patients. In only 1/65 patients (1.5%) was hippocampal atrophy reported. Across the two phases of the TIME project, structural abnormalities were identified in only 4.6% of patients.

7.4 DISCUSSION

Epileptic seizures in dementia affect a population that is significantly older than the population in whom TEA presents. These patients also perform worse than those with TEA on cognitive testing (ACE-III). Whilst there are some similarities in the seizure semiology of these patients, those that experience epileptic seizures as a feature of their dementia are more likely to report episodes of unresponsiveness, and less likely to describe olfactory hallucinations and clear episodes of amnesia on waking than patients with TEA. Imaging investigations are usually normal in TEA, whilst in dementia and MCI focal or global atrophy, and changes in keeping with small vessel disease are common. In the following section I will discuss each of these points in greater detail.

7.4.1 DEMOGRAPHIC FEATURES

Patients with TEA are younger than those with MCI and dementia who develop epileptic seizures. The mean age of onset of TEA is less than 62 years old. This is much younger than the average age of onset of epileptic seizures in our cohort, as well as global data for the onset of dementia (Qiu et al., 2009, Roberts and Knopman, 2013, Rizzi et al., 2014). However, there is an overlap between these two groups. 55/115 patients in our combined TIME cohort describe onset of seizures when aged 65 or older. Patients with the familial / early-onset form of AD do develop dementia at a younger age, typically in the 4^{th} to 6^{th} decades (Cabrejo et al., 2006, Rudzinski et al., 2008, Roberts and Knopman, 2013, Rizzi et al., 2014). Epileptic seizures are more common in this group of patients (Amatniek et al., 2006, Larner and Doran, 2009, Larner, 2011, Ryan et al., 2016). However, these patients represent only around 5% of patients with AD (Hugo and Ganguli, 2014, Ryan et al., 2016). Moreover, whist I did not find that patients with sporadic AD who developed epilepsy were younger than those that did not, this has been found in previous research (Amatniek et al., 2006, Sen et al., 2018). Consequently, whilst in our cohorts age of seizure onset is significantly higher in the dementia group than in TEA patients, it is clearly possible that seizures in patients with earlier onset forms of AD can commence at a far younger age, making it an uncertain discriminator of diagnosis on an individual level.

In our cohort, much the largest single cohort to date, TEA has been shown to be more common in males than females. This finding has been reproduced in several other case series (Lapenta et al., 2014, Mosbah et al., 2014, Ramanan et al., 2018). This is in contrast to epilepsy in dementia which I have shown to be equally common in both genders, and to Alzheimer's disease in general, which is also equally prevalent in both males and females (Hugo and Ganguli, 2014, Rizzi et al., 2014, Frisoni et al., 2017). However, in our review of the recent TEA literature, the prevalence of TEA is not significantly different in males and females (Ioannidis et al., 2011, Burkholder et al., 2017, Lanzone et al., 2018).

7.4.2 COGNITIVE TEST PERFORMANCE

Whilst patients with TEA report persistent impairment of memory it is clear from cognitive testing using ACE-III that performance is significantly better overall, and in all domains tested, when compared to patients who experience seizures as a feature of their dementia. Whilst patients with TEA can show impairment on standard memory measures, this rarely meets the diagnostic criteria for MCI or dementia, and in many cases only becomes apparent over longer delays of hours or days (Muhlert et al., 2010, Atherton et al., 2014, Elliott et al., 2014, Lanzone et al., 2018).

I have also shown that patients with dementia and a clinical suspicion of epilepsy exhibit significant decline in cognitive function over the course of 12 months. This is in contrast to patients with TEA, for whom cognitive function remains substantially stable over many years (even as many as 20), with decline as a rule only in keeping with age-related changes (Savage et al., 2016, Savage et al., 2019a).

Our patients with MCI and dementia were significantly older at the time of cognitive testing than those with TEA. However, when compared with age-matched controls, patients with MCI and dementia demonstrate poorer cognitive function than those with TEA.

7.4.3 PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

On neuropsychological testing, patients with TEA perform better than patients with MCI, who in turn perform better than those with AD. Whilst the main focus of

this chapter is the differentiation of TEA from epilepsy in dementia, I have also been able to look at the performance on neuropsychological testing of patients with TEA and those with MCI. This issue is particularly relevant as a number of other studies have suggested that patients with MCI may exhibit ALF, or that ALF may be an early feature of Alzheimer's dementia (Larrabee et al., 1993, Walsh et al., 2014, Geurts et al., 2015, Weston et al., 2018). As expected, differences between MCI and AD were highlighted after only short delays, and in the case of the RAVLT, by failure of many AD patients to reach the learning criteria. The differences between patients with TEA and MCI were more subtle and emerged over longer delays (after 30 mins in the case of the RAVLT and RCF).

It has been shown in both phases of the TIME study that many patients with TEA perform in-line with a control population on neuropsychological tests over standard testing delays. In these studies, delays of either 3 or 7 days have been sufficient to draw out this difference. In this study, recall of patients with MCI and AD was not tested over these more extended delays as impaired performance on these tests was apparent over standard delays.

7.4.4 SEIZURE FEATURES

When compared to patients with TEA, patients with epilepsy as a feature of their MCI or dementia are more likely to experience seizures involving loss of awareness, and less likely to report olfactory hallucinations or amnestic seizures on waking.

Given that in both TEA and AD seizures have frequently been shown to originate from the temporal lobes (Liedorp et al., 2010, Vossel et al., 2013, Horvath et al., 2017), it would be possible that the seizure semiology in both conditions would be similar. The main difficulty in comparing these two groups stems from the nature of memory impairment in dementia. For patients with TEA, a transient period of amnesia, during which other cognitive functions remain unaffected represents a clear change from their usual state. However, for patients with dementia, this period of amnesia is less easily recognised, as it occurs on top of baseline cognitive impairment. Moreover, even in earlier stages of AD, other cognitive domains are likely to have a degree of impairment. Our study aimed to obtain information from reliable informants, who knew the patients well, regarding

this feature, in order to elucidate information about periods of amnesia which represented a clear and unexpected increase from their previous level, which were transient in nature, and which, as in TEA occurred in a repeating and stereotyped manner.

In TEA, 39% of patients report periods of unresponsiveness. This feature is more common in patients who experience seizures as a feature of their dementia (78%). However, unlike episodes of amnesia, which are harder to determine in these patients, episodes of unresponsiveness are clearer and more memorable, particularly in the minds of the carers and informants for these patients, who have to cope with the sequelae of these events. Nonetheless it is possible that the increased prevalence of generalised seizures and unresponsive episodes in this group represents an increased tendency for seizures to spread and become generalised when compared to patients with TEA, in whom seizures commonly remain confined to the temporal lobes (Horvath et al., 2016, Horvath et al., 2018).

In our cohort of TEA patients, I have shown that olfactory hallucinations during the ictal period are common, occurring in 43% of these patients (Butler et al., 2007). This proportion is significantly higher than in patients with epilepsy in dementia where only 2 out of 37 (5.4%) reported a similar phenomenon. However, it is not known whether this difference is a result of under-reporting in patients with MCI and dementia (as a result of the extensive memory impairments in these patients), or are a reflection of impaired olfaction. In AD, as in several other neurodegenerative diseases, patients experience a reduction in their sense of smell, even in the early stages (Kjelvik et al., 2014, Attems et al., 2015, Devanand, 2016). In is not known whether olfactory impairment has an impact on the prevalence of olfactory hallucinations in the setting of a temporal lobe epilepsy syndrome such as TEA.

7.4.4 NEURORADIOLOGICAL FINDINGS

In our study a direct comparison of neuroradiological findings is impeded by differences in the imaging modalities which have been employed. Patients with TEA have largely been investigated with MR imaging, whereas the standard memory clinic protocol for patients with dementia is to undergo a CT scan. However, I have attempted to make a comparison regarding reported rates of

atrophy in these scans as well as comments regarding other abnormalities and vascular changes. Our cohorts have shown that MRI scans are typically normal in TEA, with structural abnormalities having been reported in only 4.6%. This is in contrast to patients with epilepsy in dementia where CT scans reported atrophy in 78.4%, small vessel disease in 62.2% and focal abnormalities in 16.2%. However, comparison between these two groups is made more difficult by the difference in age in these two cohorts. The increased incidence of small vessel ischaemia and generalised involutional changes in these patients may relate in part to their advanced age. Focal lesions were also uncommon in the PrESIDe epilepsy population, again suggesting that seizures in these patients are more likely to be related to the underlying pathology of their dementia rather than a single structural lesion. Several different mechanisms for epileptogenesis have been proposed for patients with Alzheimer's disease. These include tau-mediated excitotoxicity (Decker et al., 2016), alterations in voltage-gated ion channels (Verret et al., 2012) and hyper-excitability related to structural alteration of dendrites (Siskova et al., 2014) - none of which would be expected to be identified on standard CT or even MR imaging.

In addition to the above several studies have reported MRI findings in patients with AD, and in particular patients with dementia and epilepsy (Vemuri et al., 2009, Madhavan et al., 2013, Vossel et al., 2017). These studies support the findings identified on CT in our patients, and further support the differences between these imaging investigations in patients with TEA and those with epilepsy in dementia.

7.5 CONCLUSION

Patients with TEA complain of memory impairment, occurring at the time of their epileptic seizures, but also between them. Prior to receiving their diagnosis, many are concerned that these symptoms may herald the onset of dementia (Table 7.5). A diagnosis of dementia is even mistakenly made in some cases prior to the correct diagnosis of TEA being provided. However, patients with TEA typically perform normally on standard neuropsychological testing, with impairments only identified when recall is tested over longer delays (>24hrs), or on measures of autobiographical memory. In this they are in contrast with patients who develop

epileptic seizures as a feature of their dementia, in whom standard cognitive testing is abnormal.

	In favour of TEA	In favour of epilepsy in dementia
Age of onset	Onset in 6-7th decades	Onset in 7th-8th decades
Seizure features	Pure amnestic seizures; seizures on waking; olfactory hallucinations	Seizures feature altered responsiveness
Cognitive function	Normal performance on standard cognitive measures	Impaired performance on cognitive testing
Neuro-imaging	MRI normal	Atrophic changes and/or small vessel ischaemic change on CT
Prognosis	Relative stability of cognitive function over time	Clear cognitive decline over time
Treatment	Excellent response to anti-epileptic medication	Response to anti-epileptic medication unclear
Gender	More common in male sex (but see discussion)	Equal gender distribution

(Table 7.5: decision aid for diagnosing TEA vs epilepsy in dementia and MCI)

In addition, the semiology of seizures described in these patients are also different, with patients with TEA being more likely to describe features such as olfactory hallucinations and more likely to experience seizures in which transient amnesia is the sole manifestation. However, it is clear that identifying a period of amnesia is complicated by the underlying cognitive impairment in patients with dementia, and that this same problem also makes it more difficult to obtain a clear history of seizure episodes from these patients.

Cognitive decline over time in TEA is not increased when compared to an age-matched population and this stands in contrast to patients with dementia who, by definition, exhibit a progressive cognitive decline.

Seizures in TEA respond dramatically to low doses of anti-epileptic medication in the majority of patients. However, data on the use of these same medications in

dementia in terms of seizure control, side-effect profiles and cognitive decline are limited (Belcastro et al., 2007, Cumbo and Ligori, 2010). Only 1 randomised controlled trial in this group, comparing Levetiracetam, Lamotrigine and Phenobarbital, has been published (Cumbo and Ligori, 2010). This study found no significant differences in terms of efficacy, concluding that Levetiracetam was less likely to cause negative cognitive side effects than Lamotrigine, but that Lamotrigine was less likely to have a negative effect on mood. Both had a preferable side-effect profile in comparison to Phenobarbital. A Cochrane review on this topic concluded that the quality of evidence in this field was very low and should therefore be interpreted with caution (Liu et al., 2016). Further investigation of these medications in patients with a diagnosis of dementia in whom epilepsy is suspected is warranted (Larner and Marson, 2011). It would be possible to further establish differences between patients with TEA and those with epilepsy occurring as a feature of their dementia with additional tests. In the PrESIDe study, no electroencephalography was performed. Recent studies have pointed towards several features which can be identified on EEG recordings which support a diagnosis of AD (Dauwels et al., 2010, Babiloni et al., 2018, Smailovic et al., 2018, Gaubert et al., 2019). Moreover, the identification of epileptiform features on prolonged EEG recordings of patients with AD and epilepsy may help to further differentiate these patients from those with TEA (Vossel et al., 2016, Horvath et al., 2017, Horvath et al., 2018). In order to robustly differentiate patients with TEA from those with epilepsy as a feature of their dementia it would be useful to perform blinded and standardised analysis of both groups of patients using MRI and EEG. This is a potential avenue for further investigation in this field.

CHAPTER EIGHT: GENERAL DISCUSSION AND CONCLUSIONS

8.1 INTRODUCTION

In this thesis, I have described the prevalence and clinical features of epileptic seizures occurring in patients with mild cognitive impairment (MCI) and dementia, based on a study of 144 patients from the Exeter memory clinic, and a control group of 80 participants: the Presentation of Epileptic Seizures in Dementia project (PrESIDe). I have then outlined the findings of a review of these patients, 12-months after their initial assessment, in order to determine what implications epileptic seizures have for their prognosis.

Whilst it has been recognised for over a century that epileptic seizures can occur in patients with Alzheimer's disease (Stelzmann et al., 1995, Moller and Graeber, 1998), the prevalence of seizures in these patients has continued to be disputed and remains unclear (Horvath et al., 2016). I have aimed to clarify this question, through the prism of the setting in which many patients with dementia are first diagnosed, the memory clinic. Despite longstanding views that seizures occur as a feature of advanced disease in these patients (Risse et al., 1990, Volicer et al., 1995) more recent studies (Vossel et al., 2013, Sarkis et al., 2016) have argued that seizures can occur at an early stage of clinical disease, and in some patients even before memory symptoms present. This raises the possibility that seizures may not solely be a feature of advancing disease, but rather serve to accelerate the decline seen in these patients. I have investigated this question, and have shown that patients who experience epileptic seizures exhibit a more rapid decline in cognitive function than those in whom there is no clinical suspicion of epilepsy.

Alongside the PrESIDe study, I have reported the largest described cohort of patients with transient epileptic amnesia (TEA): these patients present with prominent memory difficulties in the context of epilepsy, in contrast to the patients studied through PrESIDe, who develop epilepsy in the context of a primary memory disorder. Combining 65 patients who have not previously been reported, with the 50 patients described initially by The Impairment of Memory in Epilepsy (TIME) study (Butler et al., 2007), I have clarified the demographic characteristics, seizure features and interictal cognitive symptoms of this condition. TEA remains

an under-recognised and under-reported condition. By consolidating the clinical phenotype of TEA I aim to facilitate a more prompt diagnosis in these patients, enabling treatment at an early stage, which has been shown to lead to seizure cessation in most patients (Butler et al., 2007, Mosbah et al., 2014, Lanzone et al., 2018). I have also compared our own work in the TIME study with the larger body of TEA case reports and case series in order to further clarify the nature of this condition.

Finally, I have compared these two groups of patients: those with TEA and those who experience epilepsy as a feature of their dementia, in order determine the similarities and differences between these two conditions. The aim of this comparison is to minimise diagnostic confusion. Both TEA and epilepsy in AD can be considered seizure disorders where epileptiform activity is most likely to arise from the temporal lobes (Lapenta et al., 2014, Ziyatdinova et al., 2016, Horvath et al., 2017, Lanzone et al., 2018). As a result, describing the ways in which these conditions are similar, as well as how they are different is of clear clinical value.

Patients with TEA are often concerned that the persistent memory problems that they experience may be an early feature of dementia. I have also undertaken a comparison of patients with TEA to those with MCI and AD in order to clarify the differences in their performance on neuropsychological testing, and to highlight the differences in their clinical presentations. As our clinical understanding of memory grows, and in particular our recognition of accelerated long-term forgetting (ALF) as a clinical phenomenon develops (Larrabee et al., 1993, Gascoigne et al., 2012, Elliott et al., 2014, Walsh et al., 2014) - further clarifying the differences between TEA and neurodegenerative diseases is an important task.

In this final chapter, I begin by summarising the principal findings of these studies in turn. I then highlight a number of outstanding questions and propose some directions for future investigation.

8.2 PRINCIPAL FINDINGS

8.2.1 PREVALENCE AND CLINICAL FEATURES OF EPILEPTIC SEIZURES IN DEMENTIA AND MCI

In chapter 3 I identified an increased prevalence of epileptic seizures (12.5% to 25.7%) when compared to a non-MCI or dementia control population (1.25%).

The PrESIDe study was designed to investigate a number of unanswered questions about the prevalence and clinical features of epileptic seizures occurring in patients with dementia and MCI. 144 patients were recruited as part of this study, alongside a control group of 80 age- and gender- matched participants. The majority of participants (102/144) in the patient group were diagnosed with Alzheimer's disease. Of the remainder, 20/144 were diagnosed with MCI, 16/144 with vascular dementia, 4/144 with Lewy Body dementia, 1/144 with FTD and 1/144 with the posterior cortical atrophy (PCA) variant of AD. This patient group closely reflects the estimated prevalence of these conditions nationally (Onyike and Diehl-Schmid, 2013, Hugo and Ganguli, 2014, Rizzi et al., 2014). Moreover, the design of the memory clinic from which they were recruited closely reflects the model for these services as outlined by the National Institute for Health and Care Excellence (Bayer et al., 1987, Jolley et al., 2006). I can therefore conclude that these figures are likely to be reflected in other memory clinics designed using this same framework across the UK.

In our group I identified a clinical suspicion of epilepsy in 37/144 patients (25.7%). This figure comprises 18/144 (12.5%) in whom a diagnosis of epilepsy was felt to be probable (E-Pr), and 19/144 (13.2%) in whom it was felt to be possible (E-Po). In the remaining 107/144 (74.3%) there was no clinical evidence of epilepsy (NCEE). At the time of their initial PrESIDe assessment the patients in whom there was a clinical suspicion of epilepsy were not significantly different in terms of cognition, as measured using the Addenbrooke's Cognitive Examination - Version III (ACE-III), from the NCEE group. However, a significant difference was identified on the informant completed questionnaires used for this study. On both the Cambridge Behavioural Inventory - Revised (CBI-R) and the Clinical Dementia Rating scale (CDR), patients in whom a clinical suspicion of epilepsy

was identified scored more highly, suggesting increased care requirements, reduced independence and greater overall cognitive change in these patients.

A minority of patients with epilepsy (4/37, 10.8%) in our group described generalised tonic-clonic seizures. This is in keeping with other studies in this field which have shown this seizure semiology to be present in a minority only (Vossel et al., 2013). In PrESIDe, patients more commonly presented with focal seizure presentations: episodes of impaired awareness (28/37, 75.7%), periods of amnesia on waking (20/37, 54.1%), motor automatisms (11/37, 29.7%) and olfactory disturbance (1/37, 2.7%). These features suggest a combination of focal onset seizures with or without impaired awareness, and also some focal onset seizures with secondary generalisation. This is again in keeping with other research in this discipline which, using overnight or ambulatory EEG, have shown that patients with AD typically develop focal onset seizures, most commonly arising from the temporal lobes (Beagle et al., 2017, Horvath et al., 2017).

8.2.2 PROGNOSIS OF EPILEPTIC SEIZURES IN DEMENTIA AND MCI

After a delay of 12 months, patients with MCI and dementia in whom a clinical suspicion of epilepsy is identified show a greater decline in cognition, across all domains, than patients in whom there is no evidence of seizures.

In the second stage of PrESIDe, I followed-up patients from the original group and interviewed them once again, 12-months after their initial assessment. The aim of this phase of the study was to determine whether the presence of epileptic seizures had implications for the progression of cognitive impairment in these patients. Our goal was to identify what the prognostic value of identifying patients with epileptic seizures was and whether these changes would be apparent over a relatively short (12 month) interim period. I was able to interview 102/144 (70.8%) of the original cohort. This follow-up cohort was not significantly different to the baseline group in terms of age, gender, dementia diagnosis, or cognitive performance. At this 12-month time point, patients in whom a diagnosis of epilepsy was suspected performed significantly worse on ACE-III cognitive testing, whilst maintaining a significant difference in both the CBI-R and the CDR informant questionnaires. This difference persisted, and in fact increased in size,

when the group was limited only to patients with AD. The findings of this study provide a significant contribution to our understanding of the role played by epileptic seizures in dementia, and suggest that identifying patients who have suffered from, or who are at risk of, epileptic seizures may be an important task for clinicians in the memory clinic setting. 6/37 patients in our seizure group (16.2%) experienced their first epileptic seizure after their first memory clinic appointment (and before their initial PrESIDe assessment). At present the memory clinic service in our region runs on a single appointment basis. Having received a diagnosis, patients are not routinely reviewed by the memory service. The emergence of epileptic seizures in these patients and their concomitant accelerated cognitive decline indicates that further follow-up in these patients might be of benefit, especially if it could be shown that treatment with anti-epileptic medications could have a beneficial effect in this group.

8.2.3 EXPANDING THE CLINICAL SYNDROME OF TEA

TEA is a condition with a mean age of onset of 61.7 years (26-77). In the TIME study, men were more commonly diagnosed than women (M:F = 85:30).

It is now almost 30 years since the term TEA was first developed (Kapur, 1993), over 21 years since the diagnostic criteria were developed (Zeman et al., 1998), and 12 years since the first TIME cohort of 50 patients was described (Butler et al., 2007). In this thesis I have outlined a further cohort of 65 patients and combined these two phases of the TIME study to present a cohort of 115 patients. This is the largest group of TEA patients that has been described and enables us to more fully enumerate the clinical features of this syndrome.

Seizures in TEA typically last from 15 to 30 minutes and a seizure frequency of one per month is the most common presentation. 85% of patients experience attacks on waking and in 23.5% of cases amnesia is the sole seizure feature. A complete cessation of seizures following treatment with anti-epileptic medications is seen in 93% of patients.

The ictal characteristics described by participants of both phases of the TIME study were highly consistent. This included olfactory hallucinations (42% in TIME1 and 45% in TIME2) and motor automatisms (36% in TIME1 and 45% in

TIME2). Generalised tonic-clonic seizures were seen in a minority of both cohorts (4% in TIME1 and 10.7% in TIME2). However, brief periods of unresponsiveness were more common in the TIME2 cohort (24% in TIME1, 50% in TIME2).

Persistent interictal memory symptoms (autobiographical amnesia (AbA), ALF and topographical amnesia (TopA)) are common. MRI scanning is abnormal in only 4.6%; diagnostic epileptiform EEG abnormalities are identified in 30.6%.

Since the first descriptions of TEA, it has been clear that in addition to the seizures themselves, patients commonly experience persistent interictal memory impairments. The reported rates of AbA, ALF and TopA were all significantly higher in TIME2 than they had been in TIME1. There was also an increase in the number of participants who had reported increased emotionality - noting they had been easily moved to tears since the onset of their seizures.

I have also identified several consistent features between these two groups and the developing, international literature on this condition. There is a clear need for consistency in the identification of TEA cases, as well as a standard for the neuropsychological examination of these patients. In our review of the TEA literature I found that it was often difficult, if not impossible to directly compare different case studies and case series. However, from our review of the literature I have shown that TEA is a condition that most commonly presents in patients in the 6th and 7th decades (Lapenta et al., 2014, Mosbah et al., 2014, Lanzone et al., 2018). Whilst the case series of TEA have shown an increased prevalence in men, overall the literature indicates that there is no significant difference in prevalence between male and female patients. Patients with TEA typically have normal MRI scans, with no evidence of focal abnormalities (Mosbah et al., 2014, Ramanan et al., 2018), and EEG abnormalities were identified in >50% of patients in the literature (Lanzone et al., 2018, Ramanan et al., 2018).

8.2.4 A COMPARISON OF TEA VS EPILEPSY IN DEMENTIA AND MCI

Patients with TEA are younger than those who experience epileptic seizures as a feature of MCI or dementia. They perform significantly better on cognitive testing, and imaging investigations are more likely to be

normal. In TEA, transient amnesia is more likely to be the sole manifestation of a seizure; olfactory hallucination is also more commonly reported in this group. Patients who develop epileptic seizures as a feature of MCI or dementia are more likely to experience seizures where altered responsiveness / behavioural arrest is a feature. **Patients with dementia demonstrate a clear progression of their cognitive decline, whereas those with TEA, exhibit stable cognitive performance, with decline in keeping with age related changes.**

TEA is an epilepsy syndrome in which patients describe both ictal and inter-ictal memory disturbances, suggesting temporal lobe involvement. Alzheimer's disease is a dementia, the pathological features of which appear in the temporal lobes in their earliest stages, and during which, in some patients, epileptic seizures develop. It is clear that these two conditions overlap in several ways, and in this thesis I have been able to compare these two groups in order to better understand these intersections, as well as points in which they diverge, in order to expedite the diagnostic process in the clinical setting. This is important as a diagnosis of TEA is often delayed for several years from the onset of seizures (Butler et al., 2007), with many patients mistakenly being diagnosed with dementia, and many others fearing that this may be the cause of their memory impairment. Moreover, the under-recognition of epileptic seizures in dementia misses the opportunity to identify patients who are at a greater risk of a more accelerated cognitive decline and the chance to initiate antiepileptic treatment.

I have also compared the neuropsychological performance of patients with TEA against those with MCI and a further group of patients with AD. In this comparison there were clear differences between all three groups. The performance of patients with AD was clearly worse than those with MCI and TEA on tests of verbal memory (RAVLT), visual memory (RCF) and on tests of executive function and attention (TMT and digit span). Patients with MCI and TEA performed similarly on digit span and TMT version B. However, on tests of memory, over a relatively short interval (RAVLT and RCF - both after a 30 minute delay), clear differences emerged, with patients with TEA outperforming their MCI counterparts.

8.3 OUTSTANDING QUESTIONS AND SUGGESTIONS FOR FUTURE WORK

8.3.1 EPILEPTIC SEIZURES IN DEMENTIA AND MCI

I have shown an increased prevalence of epileptic seizures in a population with MCI and dementia, when compared to an age-matched cognitively normal control population. However, there remain unanswered questions. What is the aetiology of seizures in this population? Do seizures occur as a result of a more rapidly progressive form of disease in which epilepsy is a feature, or are they a driver for an accelerated decline? These questions are not easily answered. There are several potential fields that could shed light on them.

8.3.1.1 GENETIC ANALYSIS

If seizures occurring in these patients are a consequence of, rather than a cause of, a more rapidly progressive form of AD, it is possible that the causes of this more rapid decline are genetic. Looking, for example, at the proportion of patients with epilepsy who are APOE4 carriers might be one way of investigating this. A recent study has identified links between the prevalence of epilepsy and APOE status, indicating an increased risk with the APOE4 genotype (Liang et al., 2019). It would also be possible to look at the rate of other genetic and epigenetic factors, associated with a more rapid rate of decline in AD, and whether these have an increased prevalence in patients who demonstrate epileptic seizures. Over the last decade several large scale studies have increased our understanding of the polygenic nature of AD, and the variable effects and degrees of penetrance of these changes (Lambert et al., 2013, Chouraki and Seshadri, 2014, Karch and Goate, 2015). An understanding of how these relate to epilepsy in these populations may help to explain why some patients experience seizures and others do not.

8.3.1.2 NEUROIMAGING AND CEREBROSPINAL FLUID

Developments in neuroimaging technologies have provided valuable insights in to the progression of cognitive impairment in dementia, and in particular in AD (Gordon et al., 2019, Krell-Roesch et al., 2016, Jack et al., 2018). These technologies could be used to better understand the phenomenon of epileptic seizures in dementia. A prospective study of patients with AD, both before and

following the onset of epileptic seizures could help to determine whether those who experience epileptic seizures are experiencing a form of disease which is more rapidly progressive from the outset, or whether the rate of decline only accelerates following the onset of seizures. A study of this nature could use both neuropsychological markers, as well as neuroradiology and CSF markers in order to measure these changes. In a recent study, it has been found that patients with AD who experience seizures have higher levels of CSF tau than those that do not (Tabuas-Pereira et al., 2019). An increase in this biomarker supports the idea that these patients are progressing more rapidly, that their disease is more destructive and associated with a more rapid accumulation of the pathological features of AD. However, from these data it remains unclear whether the seizures in these patients are a cause, or a result, of this more aggressive disease phenotype.

8.3.1.3 NEUROPHYSIOLOGY

In order to answer these questions a better understanding of the causes and consequences of seizures in these populations is needed. This will require increases in our knowledge of these problems on a cellular level. Important work in the field of cellular electrophysiology is beginning to unpick the effects of seizures - both in terms of the spread of tau, and other mechanisms - such as microglial activation (Yang et al., 2010, Hiragi et al., 2018), in a way which may build the case for epileptic seizures as a key driver of cognitive decline in these patients. To a large extent, our understanding of epilepsy occurring in dementia is derived from mouse models of AD (Palop et al., 2007, Palop and Mucke, 2009). It is possible that these same models may help to provide further information regarding the pathophysiology of seizures. The J20 mouse model over-expresses amyloid precursor protein (APP), leading to large increases in Aβ deposition (Mucke et al., 2000, Yang et al., 2010). Whilst we know that some mice with the J20 mutation experience seizures, we know that some don’t, and improvements in our understanding of the reasons for this are likely to impact on our understanding of disease in humans also. Studies in neurophysiology have also helped to increase our understanding of how pathology spreads in AD. Whilst some studies have suggested that the spread is primarily trans-neuronal, using a prion-like paradigm (Su et al., 1997, Lewis and Dickson, 2016, Cope et al., 2018), others have pointed towards trans-synaptic spread (Liu et al., 2012,

Pooler et al., 2013, Dujardin et al., 2014, Wang et al., 2017). In both models it has been shown that the spread of tau leads to increased neuronal excitability, potentially decreasing the seizure threshold (Brown et al., 2011, Booth et al., 2016, Das et al., 2018).

8.3.1.4 EPIDEMIOLOGY

Previous studies have shown that epileptic seizures are more common in younger AD patients, even when those with the most common genetic / familial causes of AD are excluded (Amatniek et al., 2006, Sherzai et al., 2014, Cook et al., 2015, Beagle et al., 2017). The reasons for this are unclear, although it is typically thought that patients with earlier onset of AD symptoms often do have a more rapidly progressive form of disease (Wattmo and Wallin, 2017, Tellechea et al., 2018). It has also been shown that the incidence of a first seizure is higher in more advanced disease (Romanelli et al., 1990, Mendez et al., 1994). However, in the PrESIDe study I did not find a significant difference in the age of patients with seizures compared to those in whom there was no suspicion of epilepsy. It is possible that the reasons for this lie in the method of recruitment to our study. It could be that younger patients, especially those experiencing epileptic seizures are diagnosed with AD in a setting other than the memory clinic. It also possible that the brains of younger patients make them especially at risk of experiencing a more aggressive form of AD, and developing seizures. Studies have shown that the functional connectivity of neurons decreases with age (Cope et al., 2018, Franzmeier et al., 2019). Further studies have suggested that the 3 and 4 repeat helical tau fragments which are seen in AD have a particular affinity for the most connected ‘hub’ neurons, and the most metabolically active networks (Schultz et al., 2017, Cope et al., 2018, Maass et al., 2019). This suggests that it is this connectedness of younger brains that makes them most at risk of aggressive disease, and, as a result, of developing epileptic seizures. However, the role that seizures play in these patients is not clear: it is possible that they could be a result of rapid decline, or a driver of it.

8.3.1.5 ELECTROENCEPHALOGRAPHY

In the PrESIDe study, a suspicion of epilepsy was based on the clinical history obtained from the participant and their informant. However, subclinical

epileptiform activity has been identified in several studies of dementia (Vossel et al., 2016, Horvath et al., 2017). As a consequence EEG recording in our patients could further increase estimates of the prevalence of seizures in this population. Moreover, EEG recording could also help to support an epilepsy diagnosis where there remains clinical doubt (i.e. the E-Po population). However, several studies have shown that routine clinical EEG may fail detect epileptiform activity in these patients (Vossel et al., 2016, Horvath et al., 2017). It has been shown that prolonged EEG recording, recording during sleep and the addition of magnetencephalography increases the sensitivity of this investigation (Vossel et al., 2013, Horvath et al., 2016, Horvath et al., 2018). Ideally, therefore, the most useful study in this area would be one that combined 72 hour EEG recording, with MEG recording and that these data were analysed in a systematic way by someone blinded to the presence or absence of a clinical suspicion of epilepsy in these patients. Moreover, the clinical significance of subclinical epileptiform activity, particularly in patients with MCI and dementia remains unclear (So, 2010, Lv et al., 2013, Vossel et al., 2016). Further investigation is needed to determine how far we should go to look for these abnormalities and how aggressively they should be treated.

8.3.1.6 ROLE OF ANTI-EPILEPTIC MEDICATION

I have not directly studied the important question of whether the use of anti-epileptic medications in these patients has an effect on prognosis in patients who develop epileptic seizures as a feature of MCI or dementia. If epileptic seizures are a cause of a more accelerated decline in these patients it is possible that the use of anti-epileptic medications could have an impact on their rate of decline over time. Whilst many of our participants had not previously been identified as having had epileptic seizure, I also encountered patients in whom a suspicion of epilepsy was identified, but for whom no treatment was given. This was felt to relate to both an uncertain efficacy for this treatment in terms of the progression of their disease, but also, more commonly, a reluctance to prescribe these medications due to concerns regarding their possible cognitive side effects. Whilst there is extensive evidence that older anti-epileptic treatments (Phenytoin, Carbamazepine, Sodium Valproate, Phenobarbital) commonly have a negative impact on cognition (Vermeulen and Aldenkamp, 1995, Park and Kwon, 2008), the same is not true of newer treatments (Lamotrigine, Levetiracetam). There is

no robust evidence to support withholding treatment for epilepsy in these patients based on concerns about the potential for cognitive impairment. However, a recent study has identified an increased risk of pneumonia in patients with AD treated with anti-epileptic medications (Taipale et al., 2019), suggesting that these treatments are not risk free in this population.

A recent Cochrane review on this topic found both Lamotrigine and Levetiracetam to be effective treatments for epileptic seizures in these patients (Liu et al., 2016). However, these findings were based on only one randomised controlled trial (Cumbo and Ligori, 2010). It concluded that, of these two, Levetiracetam was less likely to be associated with cognitive impairment, but more likely to be associated with a negative impact on mood, when compared to Lamotrigine. However, it is less clear whether either of these medications may reduce the progression of cognitive decline in these patients. There is experimental evidence, again largely from mouse models of AD, that Levetiracetam reduces the neuronal hyperexcitability seen in these patients (Sanchez et al., 2012, Musaeus et al., 2017). Studies which have investigated the potential neuroprotective effects of Levetiracetam, and related drugs, have failed to find significant evidence for its use for this indication across all patients with MCI or dementia (Devi and Ohno, 2013, Nygaard et al., 2015, Inaba et al., 2019), although further investigations are ongoing (Vossel, 2019). A randomised double-blind study, comparing the use of anti-epileptic medication, with placebo, in these patients could help to determine whether their use may be associated with a slower decline which would encourage their use in a clinical setting.

8.3.1.7 PROGNOSIS

In the PrESIDe study, I have been able to conclude that patients who experience epileptic seizures as a feature of MCI or dementia, exhibit an accelerated rate of cognitive decline when compared to patients in whom there is no suspicion of epilepsy. However, the duration of follow-up in this study was limited to 12-months after their baseline study assessment. It would be useful to have a study with a more prolonged period of follow-up that would enable us to assess whether this more rapid rate of decline was sustained. This is particularly true in terms of other markers of cognitive decline (increasing requirements for care support at

home, admission to nursing or residential homes and mortality) which may also be increased in these patients.

8.3.2 TEA

8.3.2.1 ONGOING PROJECTS: PROGNOSIS &TREATMENT STUDIES

It is over 12 years since the initial publication of the first TIME series of 50 patients with TEA (Butler et al., 2007). There is now extensive longitudinal follow-up information for this group of patients. Furthermore, 10/50 patients in this original cohort were initially seen as part of an earlier study, and for many patients more than 20 years of follow-up data are available (Savage et al., 2016). As a result of this there is a great opportunity to investigate and to describe the long term features of TEA; including the evolution of the interictal memory impairments described in this condition, the long term control of seizures, as well as other features - such as emotional lability, and olfactory dysfunction - which the TIME participants have described. Several studies have examined the long-term cognitive sequelae of temporal lobe epilepsy, and identified similar features in both neuropsychological and pathologic terms, with Alzheimer's disease (Helmstaedter and Elger, 2009, Thom et al., 2011, Tai et al., 2016, Caciagli et al., 2017). Investigating the long term effects of TEA, a form of temporal lobe epilepsy in which the main ictal feature is memory impairment, is particularly pertinent.

I have shown that commonly prescribed anti-epileptic medications (including Levetiracetam, Lamotrigine, Sodium Valproate and Carbamazepine) effectively control seizures in patients with TEA. However, it is less clear whether these treatments also lead to an improvement of the interictal memory symptoms described by these patients. Such information is of great interest as, for many patients with TEA, these interictal features have a great impact on their day-to-day lives. The TIME team has recently concluded a study investigating the effects of treatment on these features. Through neuropsychological testing of patients prior to starting treatment, and again 6 months later, once seizure control has been established, we are able to better understand the effects of anti-epileptic treatment. From meeting with TEA patients, as part of a TIME research day in 2018, one of the key questions study participants and their families wanted to know about was which medication is best for them - in terms of seizure control,

side-effects and also for the interictal memory symptoms, and a study which best answers these questions is therefore very much desired by the TEA community. Whilst several studies have compared anti-epileptic treatments in this way (Ramsay et al., 2008, Brigo et al., 2016, Meador et al., 2016, Meschede et al., 2018), none have focussed on the particular cognitive symptoms experienced by patients with TEA. Given that TEA is a relatively uncommon condition, such a study is unlikely to be possible. However the TIME treatment study will provide useful information and will enable us to advise our patients, as well as other clinicians, on the potential benefits of prompt anti-epileptic treatment.

8.3.2.2 TOPOGRAPHICAL MEMORY

During the first phase of the TIME project it became clear that patients with TEA frequently experienced difficulties with navigation, this phenomenon was described in 36% of these patients. On further questioning, it became clear that this topographical memory impairment related to navigation of familiar routes and journeys and the recognition of landmarks. Patients frequently have a sense of unfamiliarity whilst on a journey that they have taken several times before. The role of the hippocampus in navigational tasks and spatial memory is well established (Maguire et al., 2000, Maguire et al., 2006, Hartley et al., 2007, Maguire et al., 2016). However, the precise nature and degree of impairment observed in patients with TEA has been difficult to evaluate on standard neuropsychological testing. More recently we have been incorporating the four mountains test to interrogate spatial memory (Chan et al., 2016). This test has been shown to identify patients with pre-Alzheimer's disease, a group in whom topographical difficulties are common (Uc et al., 2004, Moodley et al., 2015, Wood et al., 2016), with high sensitivity. Several recent studies have utilised virtual reality technology to probe navigational impairments (Salgado-Pineda et al., 2016, Cogne et al., 2017, Sato et al., 2017), in the future it would be interesting to further examine the interictal topographical memory impairment seen in TEA using these strategies.

8.3.2.3 EMOTIONAL LABILITY

26/65 (40%) patients with TEA in TIME2 reported that they had been aware of a change in their emotional responses since the onset of their epileptic seizures. In

most cases (24/65, 37%) this change took the form of being more easily moved to tears, in the setting of films, books or television programmes, but also to real life events. The physiology underlying this symptom is unclear, although it is thought to relate to changes to medial temporal lobe connections. A similar phenomenon has been described in the setting of autoimmune encephalitides, which also affect the mesial temporal lobes (Al-Diwani et al., 2019). However, in these patients a far broader range of neuropsychiatric presentations has been reported (Kayser et al., 2013, Gibson et al., 2019). In TIME, whilst this feature was often described by patients, it has not yet been investigated. Moreover, it has not consistently been reported by other case series or case reports of TEA. A systematic study of these altered emotional responses, involving both patient and informants, and relating these to underlying neurobiological mechanisms, would be of interest. Several tools have been designed to ask about mood (Bjelland et al., 2002, Smarr and Keefer, 2011). However, whilst depression is common in temporal lobe epilepsy (Orjuela-Rojas et al., 2015, Vrinda et al., 2017), patients with TEA do not consistently report changes in their mood - as evidenced by our own findings on HADS questionnaires.

8.3.2.4 ELECTROENCEPHALOGRAPHY IN TEA

Several studies have shown that increased periods of EEG recording increase the detection rate for interictal epileptiform abnormalities (Werhahn et al., 2015, Burkholder et al., 2016), particularly when this recording is performed during sleep (Malow et al., 1999, Malow et al., 1998, Liu et al., 2018). In order to more thoroughly and systematically report on the EEG findings in these patients it would be useful to have prolonged EEG recordings, with periods of sleep and wakefulness, in all patients, and for these to be analysed in a consistent way (i.e. by a specific rater or raters), using validated criteria and more sophisticated techniques of network analysis. Moreover given that EEG analysis of deep medial temporal structures is often limited, other modalities may be useful - such as magnetoencephalography (MEG) (Baumgartner et al., 2000, Pizzo et al., 2019). Although even when this technology is available, the medial temporal lobe often still appears to be resistant to interrogation (Wennberg et al., 2011, Tamilia et al., 2017). In addition, a more recent development, optically-pumped magnetometers (OPMs), have shown promise in facilitating mobile MEG equipment to be used whilst patients undergo tasks in a virtual reality environment (Boto et al., 2019,

Roberts et al., 2019). The use of new technologies, such as OPM-MEG, particularly in topographical and autobiographical memory tasks would be particularly useful in these patients.

8.3.2.5 GENETICS OF TEA

Recent years have seen a rapid expansion in our understanding of the genetic basis of epilepsy. Several studies have identified genes which increase the risk of seizures and others which decrease it (Hildebrand et al., 2013, Moller et al., 2015, Magalhaes et al., 2019). These studies have shown that there will be a genetic contribution to most epilepsies. An understanding of the genetics of what were previously thought of as 'idiopathic' epilepsies also has implications for the treatment of these conditions (Scheffer, 2014, Balestrini and Sisodiya, 2018). At present no studies have looked at the genetic make-up of patients with TEA. However, the TIME team is increasingly collecting these data from participants in order to better understanding the pathophysiology of this condition and large scale, multi-centre studies of TEA will be required in order to establish a large enough cohort of patients to adequately power this research, and to reach definitive conclusions.

8.3.2.6 POST-MORTEM EXAMINATION OF TEA PATIENTS

EEG and MRI have identified focal structural abnormalities in only a minority of patients with TEA (Mosbah et al., 2014, Lapenta et al., 2014, Lanzone et al., 2018). However, to date there have been no post-mortem studies of patients with TEA. Many participants of the TIME study have been kind enough to volunteer to donate their brains to science and research such as this will likely help us to better understand the underlying pathology of this condition and the long term effects of seizures in this population. Several post-mortem studies have shown an increased deposition of the pathological features of AD, Aβ and tau, in patients with epilepsy (Tai et al., 2016, Tai et al., 2018, Machado et al., 2019). A similar examination of the brains of patients with TEA would prove useful, in order to determine whether TIME project participants may also show these changes, and whether they correlate with the degree of memory impairment seen in these patients. Advances in tau-PET imaging, which have shown how well the deposition of tau correlates with cognitive decline in more classical tauopathies

(Ossenkoppele et al., 2016, Jack et al., 2018, Gordon et al., 2019), may lead to this also proving a useful tool in TEA.

8.4 CONCLUSIONS

As the global population ages there has been a commensurate increase in the prevalence of MCI and dementia. Whilst our understanding of these conditions increases, multiple drug trials have failed to identify disease modifying treatments for AD, or other forms of dementia (De Strooper, 2014, Cummings et al., 2019). Increasing evidence implicates early and mid-life modifiable risk factors in the development of AD, including diet, exercise and blood pressure (Lane et al., Lourida et al., 2019). Whilst the end product of all forms of dementia, regardless of risk factors, is progressive cognitive impairment, it is clear that the trajectory these patients take as their impairments accrue can vary significantly. For some patients the reasons for this will be genetic, for others lifestyle and environmental factors will play a significant role. For others the development of epileptic seizures, perhaps as a result of a dementia which was already more rapidly progressive, accelerates the decline further still. The utilisation of new and emerging technologies to better understand why this happens, and to further investigate the impact of anti-epileptic treatments in these patients may identify potential avenues for new treatments in these patients.

In this thesis I have shown an increased prevalence of epilepsy in patients with MCI and dementia. I have shown that these patients are no different than those in whom there is no evidence of epilepsy in terms of age or cognitive function at the time of their diagnosis. I have gone on to show that cognitive decline occurs more rapidly in patients with epilepsy and that their level of disability is greater, as evidenced by CDR and CBI-R. Whilst the problem of epileptic seizures occurring in dementia is not a new one, it is attracting increasing interest. Research in this field is providing valuable insights into the pathophysiology of dementia. However, whether seizures are a cause of this accelerated decline, or a marker of it, requires further study.

Patients with TEA report transient periods of impaired memory, but also persistent interictal memory difficulties. In these patients seizures frequently occur on waking, and on a monthly basis. Whilst amnesia is often the sole feature

of a seizure, in around 40% of patients, olfactory hallucinations are seen. Patients with TEA commonly report interictal memory features including AbA, ALF and TopA. In TIME2 these features were all present in >70% of cases. I have reported on the largest cohort of TEA patients to date, and in doing so have further consolidated the phenotype of this epilepsy syndrome.

Finally, I have shown how patients with TEA are different from those who experience epileptic seizures as a feature of MCI or dementia. Patients with TEA are typically younger and demonstrate less impairment on neuropsychological testing. Patients who experience epileptic seizures as a feature of MCI or dementia are more likely to report episodes of loss of consciousness and less likely to experience seizures on waking or olfactory hallucinations. These patients show an accelerated rate of cognitive decline, and their increased impairments place an increased demand for care from those closest to them. The prompt recognition of these patients is an important duty for clinicians tasked with their care.

APPENDICES

APPENDIX 1: PrESIDe DATA COLLECTION FORM

Epileptic seizures in Dementia and MCI

Interviewer		Interview_date	
Place_of_interview		Interview_time	

First_name		DOB	
Last_name		Age_when_seen	
Study_ID			

dementia details

ACE-III			
date_seen_in_mem_clinic		Mem_clinic_Diagnosis	
Duration_of_symptoms		age_at_onset	

		Describe an example
memory_difficulties	YES/ NO	
visuospatial_problems	YES/ NO	
organisational_problems	YES/ NO	
language_ problems	YES/ NO	
arithmetical problems	YES/ NO	
mood_disturbance	YES/ NO	
psychosis	YES/ NO	
sleep_disturbance	YES/ NO	
behavioural disturbance	YES/ NO	

example of memory problems	

Assessment_of_fluctuation	
One_day_fluctuation	

Study ID: Participant Initials:

fluctuation	YES/ NO	
fluctuation_example		
Loss_of_consciousness	YES/NO	
LOC_example		

Seizure features. Please indicate Y or N

Generalised seizures	YES/ NO	
Partial seizures		
Automatisms	YES/ NO	
Olfactory / gustatory hallucinations	YES/ NO	
Dejavu	YES/ NO	
Period of altered responsiveness	YES/ NO	
amnesic episodes (on waking)	YES/ NO	
amnesic episodes (at other times)	YES/ NO	
Repetitive questioning	YES/ NO	
Triggers	YES/ NO	
Aura	YES/ NO	
example seizure		

Study ID: participant Initials:

Family history

Fam_Hx_dementia	YES/ NO
Fam_Hx-Epilepsy	YES/ NO
Fam_Hx_other	
Current_medications	
Past-medical_Hx	
Birth_trauma / Anoxia	YES/ NO
birth_trauma / anoxia_details	
Febrile_seizures	YES/ NO
Febrile_seizures_details	
Significant_head_injury	YES/ NO
Head_injury_details	
Intracranial_infection	YES/ NO
Intracranial infection details	
Stroke	YES/NO
Stroke_details	
EEG	YES/ NO
EEG_result	
MRI	YES/ NO
MRI _result	
CT	YES/NO
CT_Results	

APPENDIX 2: ADDENBROOKE'S COGNITIVE EXAMINATION VERSION-III

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

Name: Date of Birth: Hospital No. or Address:	Date of testing: ___/___/___ Tester's name:_____ Age at leaving full-time education:_____ Occupation: _____ Handedness: _____

ATTENTION

➢ Ask: What is the	Day _____	Date _____	Month _____	Year _____	Season _____	**Attention** [Score 0-5] ☐
➢ Ask: Which	No./Floor _____	Street/Hospital _____	Town _____	County _____	Country _____	**Attention** [Score 0-5] ☐

ATTENTION

➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". ➢ Score *only* the first trial (repeat 3 times if necessary). ➢ Register number of trials: _____	**Attention** [Score 0-3] ☐

ATTENTION

➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." ➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4). ➢ Stop after five subtractions (93, 86, 79, 72, 65): ____ ____ ____ ____ ____	**Attention** [Score 0-5] ☐

MEMORY

➢ Ask: 'Which 3 words did I ask you to repeat and remember?' _____ _____ _____	**Memory** [Score 0-3] ☐

FLUENCY

➢ **Letters** Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".	**Fluency** [Score 0 – 7] ☐

				≥ 18	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				0-1	0
				total	correct

➢ **Animals** Say: "Now can you name as many animals as possible. It can begin with any letter."	**Fluency** [Score 0 – 7] ☐

				≥ 22	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

MEMORY

➢ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

Memory [Score 0 – 7] ☐

	1st Trial	*2nd Trial*	*3rd Trial*
Harry Barnes 73 Orchard Close Kingsbridge Devon	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____

MEMORY

➢ Name of the current Prime Minister.....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president.....
➢ Name of the USA president who was assassinated in the 1960s.....

Memory [Score 0 – 4] ☐

LANGUAGE

➢ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "**Pick up the pencil and then the paper**." If incorrect, score 0 and do not continue further.

➢ If the subject is correct on the practice trial, continue with the following three commands below.
- Ask the subject to "**Place the paper on top of the pencil**"
- Ask the subject to "**Pick up the pencil but not the paper**"
- Ask the subject to "**Pass me the pencil after touching the paper**"

Note: Place the pencil and paper in front of the subject before each command.

Language [Score 0-3] ☐

LANGUAGE

➢ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations.
Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

Language [Score 0-2] ☐

LANGUAGE

➢ Ask the subject to repeat: **'caterpillar'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.

Language [Score 0-2] ☐

LANGUAGE

- Ask the subject to repeat: **'All that glitters is not gold'**

Language [Score 0-1] ☐

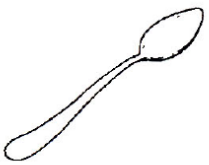
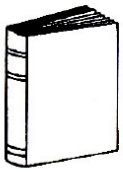
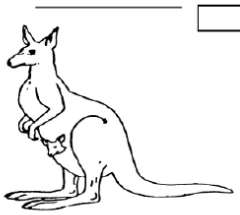
- Ask the subject to repeat: **'A stitch in time saves nine'**

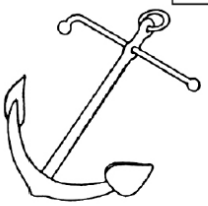
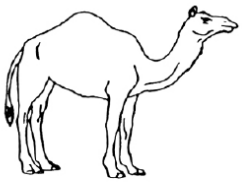
Language [Score 0-1] ☐

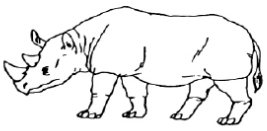
LANGUAGE

- Ask the subject to name the following pictures:

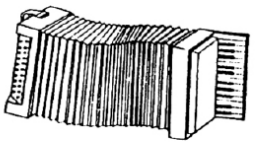
Language [Score 0-12] ☐







LANGUAGE

- Using the pictures above, ask the subject to:

Language [Score 0-4] ☐

- Point to the one which is associated with the monarchy .....
- Point to the one which is a marsupial .....
- Point to the one which is found in the Antarctic .....
- Point to the one which has a nautical connection .....

Updated 20/11/2012

LANGUAGE

- Ask the subject to read the following words: (Score 1 only if all correct)

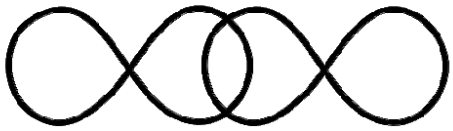
Language [Score 0-1] ☐

sew
pint
soot
dough
height

VISUOSPATIAL ABILITIES

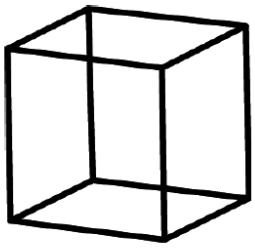
- Infinity Diagram: Ask the subject to copy this diagram

Visuospatial [Score 0-1] ☐



- Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).

Visuospatial [Score 0-2] ☐



- Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).

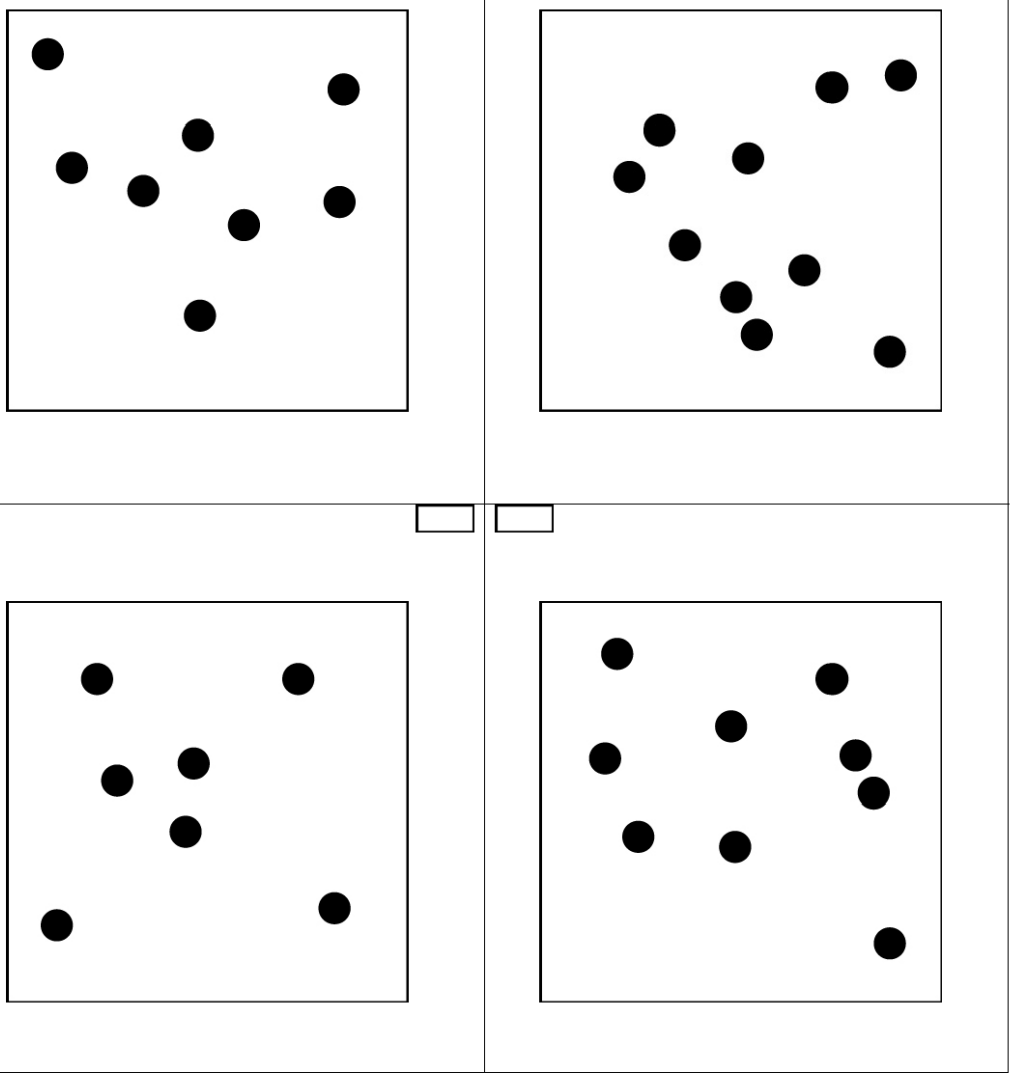
Visuospatial [Score 0-5] ☐

Updated 20/11/2012

VISUOSPATIAL ABILITIES

- Ask the subject to count the dots without pointing to them

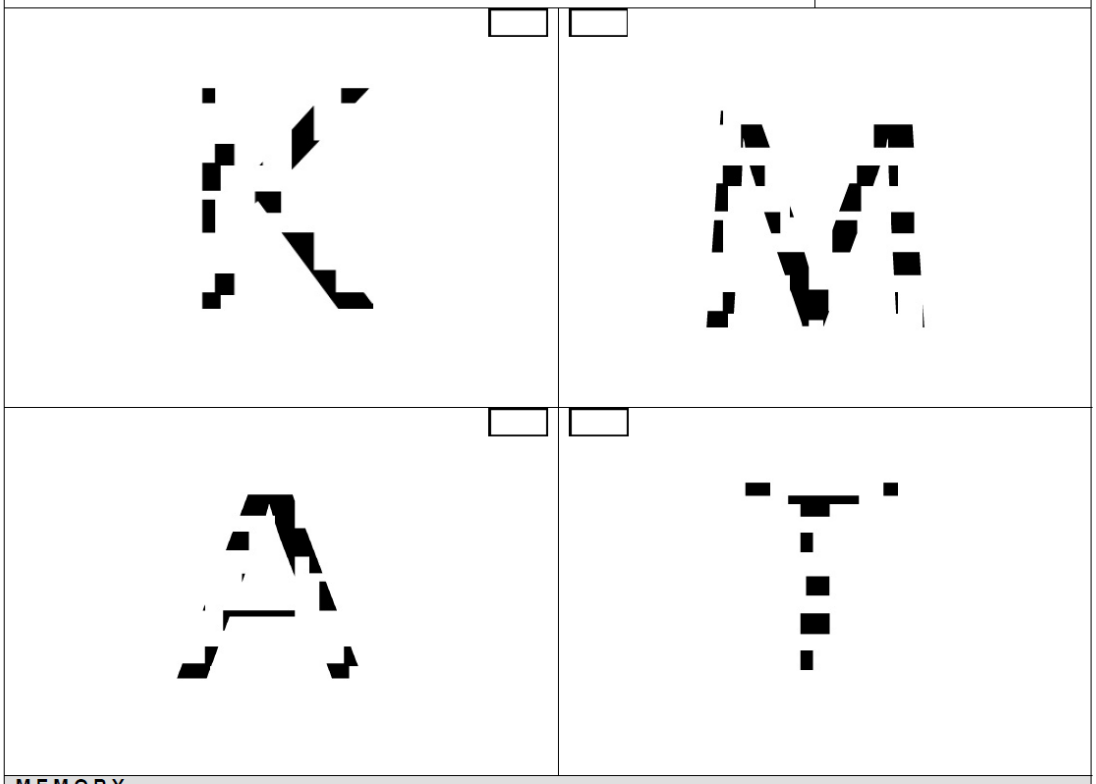
Visuospatial
[Score 0-4]



VISUOSPATIAL ABILITIES

➢ Ask the subject to identify the letters

Visuospatial [Score 0-4] ☐



MEMORY

➢ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"

Harry Barnes 73 Orchard Close Kingsbridge Devon	……. …… …… ……. …… …… ……	**Memory** [Score 0-7] ☐

MEMORY

➢ This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.

Memory [Score 0-5] ☐

Jerry Barnes	☐	Harry Barnes	☐	Harry Bradford	☐	recalled	☐
37	☐	73	☐	76	☐	recalled	☐
Orchard Place	☐	Oak Close	☐	Orchard Close	☐	recalled	☐
Oakhampton	☐	Kingsbridge	☐	Dartington	☐	recalled	☐
Devon	☐	Dorset	☐	Somerset	☐	recalled	☐

SCORES

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

Updated 20/11/2012

APPENDIX 3: CAMBRIDGE BEHAVIOURAL INVENTORY - REVISED

Cambridge Behavioural Inventory Revised (CBI-R)

For the Carer

Your Name:_____ Today's date:___/___/___
Patient's name: _____Relationship to the patient_____

We would like to ask you a number of questions about various changes in the patient's behaviour that you may have noticed. It is important that we obtain your view as it will help us in our assessment.
Please read the description of each problem carefully. Then circle the number under the heading "Frequency" that best describes the occurrence of the behavioural change.
Some of the everyday skill questions may not apply, if for instance the person you care for has never done the shopping. Please enter N/A (not applicable).

All questions apply to the patient's behaviour OVER THE PAST MONTH.

0 Never	1 a few times per month	2 a few times per week	3 daily	4 constantly

	FREQUENCY				
Memory and Orientation					
Has poor day-to-day memory (e.g. about conversations, trips etc.)	0	1	2	3	4
Asks the same questions over and over again	0	1	2	3	4
Loses or misplaces things	0	1	2	3	4
Forgets the names of familiar people	0	1	2	3	4
Forgets the names of objects and things	0	1	2	3	4
Shows poor concentration when reading or watching television	0	1	2	3	4
Forgets what day it is	0	1	2	3	4
Becomes confused or muddled in unusual surroundings	0	1	2	3	4
Everyday Skills					
Has difficulties using electrical appliances (e.g. TV, radio, cooker, washing machine)	0	1	2	3	4
Has difficulties writing (letters, Christmas cards, lists etc.)	0	1	2	3	4
Has difficulties using the telephone	0	1	2	3	4
Has difficulties making a hot drink (e.g. tea/coffee)	0	1	2	3	4
Has problems handling money or paying bills	0	1	2	3	4
Self Care					
Has difficulties grooming self (e.g. shaving or putting on make-up)	0	1	2	3	4
Has difficulties dressing self	0	1	2	3	4
Has problems feeding self without assistance	0	1	2	3	4
Has problems bathing or showering self	0	1	2	3	4
Abnormal Behaviour					
Finds humour or laughs at things others do not find funny	0	1	2	3	4
Has temper outbursts	0	1	2	3	4
Is uncooperative when asked to do something	0	1	2	3	4
Shows socially embarrassing behaviour	0	1	2	3	4
Makes tactless or suggestive remarks	0	1	2	3	4
Acts impulsively without thinking	0	1	2	3	4

Cambridge Behavioural Inventory Revised (CBI-R)

0 Never	1 a few times per month	2 a few times per week	3 daily	4 constantly

Mood						
Cries	0	1	2	3	4	
Appears sad or depressed	0	1	2	3	4	
Is very restless or agitated	0	1	2	3	4	
Is very irritable	0	1	2	3	4	
Beliefs						
Sees things that are not really there (visual hallucinations)	0	1	2	3	4	
Hears voices that are not really there (auditory hallucinations)	0	1	2	3	4	
Has odd or bizarre ideas that cannot be true	0	1	2	3	4	
Eating Habits						
Prefers sweet foods more than before	0	1	2	3	4	
Wants to eat the same foods repeatedly	0	1	2	3	4	
Her/his appetite is greater, s/he eats more than before	0	1	2	3	4	
Table manners are declining e.g. stuffing food into mouth	0	1	2	3	4	
Sleep						
Sleep is disturbed at night	0	1	2	3	4	
Sleeps more by day than before (cat naps etc.)	0	1	2	3	4	
Stereotypic and Motor Behaviours						
Is rigid and fixed in her/his ideas and opinions	0	1	2	3	4	
Develops routines from which s/he can not easily be discouraged e.g. wanting to eat or go for walks at fixed times	0	1	2	3	4	
Clock watches or appears pre-occupied with time	0	1	2	3	4	
Repeatedly uses the same expression or catch phrase	0	1	2	3	4	
Motivation						
Shows less enthusiasm for his or her usual interests	0	1	2	3	4	
Shows little interest in doing new things	0	1	2	3	4	
Fails to maintain motivation to keep in contact with friends or family	0	1	2	3	4	
Appears indifferent to the worries and concerns of family members	0	1	2	3	4	
Shows reduced affection	0	1	2	3	4	

Any other comments:

Thank you for your time.

APPENDIX 4: CLINICAL DEMENTIA RATING SCALE

Please tick the ONE statement from each of the six following categories that you feel best applies to the patient:

1. Memory

a. No memory loss or slight inconsistent forgetfulness ☐
b. Mild consistent forgetfulness; has partial recollection of recent events ☐
c. Moderate memory loss more marked for recent events; interferes with everyday activities ☐
d. Severe memory loss; only highly learned material retained, new memories rapidly lost ☐
e. Severe memory loss; only fragments of memory for past remain ☐

2. Orientation

a. Fully orientated. Aware of time, day, month and place ☐
b. Some difficulty with time or day; oriented for familiar places and people, but not those which are unfamiliar ☐
c. Usually disorientated in time, often for place ☐
d. Severe disorientation except for own name ☐

3. Judgement, problem solving and decision making

a. Solves everyday problems well; judgement good in relation to past performance ☐
b. Only doubtful impairment in solving problems ☐
c. Moderate difficulty in handling complex problems ☐
d. Severely impaired in handling problems ☐
e. Unable to make judgements or solve problems ☐

4. Job, shopping, handling money, paying bills

a. Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups ☐
b. Only doubtful or mild impairment in these activities ☐
c. Unable to function independently at these activities though may still be engaged in some ☐
d. Unable to function independently outside the home ☐

5. Home (cooking, housework), hobbies, interests

a. Normal ☐
b. Only slightly impaired ☐
c. Mild but definite impairment. Difficult chores and more complicated hobbies abandoned ☐
d. Simples chores preserved; very restricted interests ☐
e. No significant function in home ☐

6. Personal care (shaving, grooming, bathing)

a. Fully capable of self-care ☐
b. Needs occasional prompting ☐
c. Requires assistance in dressing, washing, keeping personal effects ☐
d. Requires much help with personal care; often incontinent ☐

APPENDIX 5: ILLUSTRATIVE CASES FROM THE PrESIDe STUDY

Case 1 (EX125) Alzheimer's Disease (NCEE)

TF is an 86-year old retired telephonist and secretary. She was seen in the memory clinic in March 2017 with a history of progressive memory impairment which she described as 'not very bad'. However, her husband reported that he had become increasingly concerned about her, and that he could no longer rely on her short term memory. He described that if she were to answer the phone and to take a message, by the time the conversation was over, the message would have been forgotten. He felt that it was now up to him to keep track of appointments, household finances and much of the cooking at home. TF herself reported some intermittent word-finding difficulties, and in particular recognised that she would have trouble remembering the names of other couples who they would see each week at their square-dancing classes.

There had been no change in behaviour, no history of hallucinations, and both TF and her husband felt that her memory impairment was relatively consistent from one day to the next. TF denied any change in her mood although her husband felt that she could be a bit low sometimes and on other occasions might be a bit short tempered, particularly when she felt that he doubted her memory.

At her memory clinic appointment in February 2017 her ACE-III score was 77/100 (attention 17/18, memory 12/26, fluency 8/14, language 25/26, visuospatial 15/16). A CT head scan performed at that time showed evidence of mild small vessel disease and a degree of atrophic change a little in excess of what would be expected for her age.

At the time of her first PrESIDe visit (August 2017) her ACE-III score had decreased to 68/100 (attention 13/18. Memory 13/26, fluency 6/14, language 21/26, visuospatial 15/16). Her CDR-SOB score was 4.0 and her CBI-R score 37, both of which pointed in particular to problems with memory, and in the case of the CDR to definite impairments in home, hobbies and interests.

At her second visit (August 2018) there had been some further deterioration, although TF herself was not convinced - 'my husband thinks I have got worse'.

The ACE-III had decreased to 66/100 (attention 12/18, memory 12/26, fluency 6/14, language 22/26, visuospatial 14/16).

TF was diagnosed with Alzheimer's disease at her memory clinic appointment and this was confirmed using diagnostic criteria at her initial PrESIDe assessment.

Case 2 (EX132) Vascular Dementia (NCEE)

MP is a 79-year old farmer's wife, who was seen in the memory clinic in April 2017 alongside her son. He described a 12-month history of a step-wise decline in cognitive function, which had become significantly worse around the time of a fall during the previous November. At that time she was admitted to hospital and found to have atrial fibrillation. MP admitted to a 'bad memory' but felt that she was coping OK at home by herself. Her son however, had numerous concerns: she could get lost when out of the house, she struggled to learn new technology, such as the television, and could misplace things around the house. She had become increasingly reliant on her family to support her in her activities of daily living - such as preparing meals and cleaning the house.

Whilst she denied any change in behaviour, MP's son had felt that she was less motivated and had become a bit apathetic about many things. There was no history of psychosis / hallucinations and no concerns about low mood.

At her memory clinic appointment her ACE-III score was 69/100 (attention 14/18, memory 15/26, fluency 2/14, language 23/26, visuospatial 15/16). Of particular note, both category and letter fluency were slow she found it difficult to sustain attention on these tasks. Free recall was poor, but improved significantly with prompting. A CT head scan was performed and showed diffuse small vessel disease, which was more prominent in the posterior frontal lobe. An established lacunar infarct was seen in the right basal ganglia.

At the time of her first PrESIDe (September 2017) assessment her ACE-III score had dropped to 57/100 (attention 13/18, memory 12/26, fluency 1/14, language 21/26, visuospatial 10/16). This dropped further to 55/100 at her 12-month follow-up visit in September 2018 (attention 12/18, memory 12/26, fluency 0/14,

language 21/26, visuospatial 10/16). On the informant completed questionnaires there was evidence of multi-domain impairment affecting scores for memory, orientation, judgement, and home hobbies and interests on the CDR.

At her initial memory clinic appointment MP was diagnosed with vascular dementia, although it was recognised that Alzheimer's disease could not be excluded. The vascular dementia diagnosis was confirmed using diagnostic criteria at the time of her initial PrESIDe assessment.

Case 3 (EX100) Dementia with Lewy Bodies (NCEE)

BW is an 80-year old retired farmer. He was seen in the memory clinic in December 2016 alongside his wife and daughter-in-law. They reported a 3-year history of increasing concern about his memory. More recently they had also been aware of worsening slowness of his movements and a right upper-limb tremor which was present at rest. It was felt that his memory symptoms could fluctuate from one day to the next.

BW himself had good insight into his memory problems. He recognised that he would forget recent conversations and have trouble remembering appointments or when medications were due. He could misplace items around the house and needed more help with keeping track of household finances. He did have some problems with word-finding and remembering the names of people and things. There was no history of becoming lost in unfamiliar surroundings, his mood was good and he was completely independent with personal care.

At his memory clinic appointment (December 2016) his ACE-III score was 58/100 (attention 11/18, memory 15/26, fluency 3/14, language 21/26, visuospatial 8/16). A CT head scan performed at that appointment showed some very mild periventricular and basal ganglia low attenuation in keeping with minimal small vessel disease, and some generalised involutional changes which were felt to be consistent with the patient's age.

At his initial PrESIDe visit (June 2017) the ACE-III score was 63 (attention 13/18, memory 17/26, fluency 4/14, language 19/26, visuospatial 10/16). The CDR-SOB score was 5.0 and the CBI-R total score was 56. These informant completed

questionnaires pointed especially to difficulties with memory and orientation, everyday skills, sleep and motivation. At the time of this assessment BW's wife also reported two episodes of visual hallucination which had occurred in the preceding months.

The ACE-III score at the 2nd PrESIDe (June 2018) visit was 61 (attention 13/18, memory 10/26, fluency 5/14. Language 23/26, visuospatial 10/16). Whilst BW felt that his memory had been fairly stable, his wife was clear that she had had to take over more and more of the household jobs, and was now completely in charge of household finances. She was no longer comfortable with him being out of the house by himself and some further episodes of hallucination had occurred.

At the time of his memory clinic appointment a diagnosis of dementia with Lewy Bodies was suspected and this was confirmed using formal criteria at the time of his initial PrESIDe assessment.

Case 4 (EX023) Frontotemporal Dementia (NCEE)

IG is a 68-year old retired IT project manager. He was seen in the memory clinic in June 2016 alongside his wife. They reported that a three to four year history of increasing concerns about language, memory and in particular behavioural change. He was becoming increasingly frustrated by his difficulties in expressing himself and his needs. Having always been calm and mild-mannered, his family had become concerned that he was now short-tempered and verbally aggressive. He never previously used to swear, but now did so often. He was aware of difficulties with short term memory, and struggled with tasks that involved planning and sequencing - a significant change for someone whose career had demanded great proficiency on this front.

His ACE-III score at that time was 79/100 (attention 18/18, memory 16/26, fluency 7/14, language 23/26. Visuospatial 15/16). A CT head scan reported on marked atrophy of the left temporal lobe, although the right was relatively normal, and notable thinning of the gyri in both frontal lobes particularly on the left.

At his initial PrESIDe assessment (December 2016) he reported worsening language difficulties - getting 'me' and 'you' mixed-up and using increasingly short

sentences with frequent grammatical errors. On that occasion his ACE-III score was 75/100 (attention 18/18, language 18/26, fluency 4/14, language 20/26, visuospatial 15/16). The CBI-R total score of 51 and a CDR-SOB of 3.5. These questionnaires highlighted problems with judgement, changes in behaviour and difficulties with naming objects and things.

By the time of his 12-month follow-up assessment (January 2018) this score had dropped further to 55/100 (attention 14/18, memory 11/26, fluency 1/14, language 16/26, visuospatial 13/16). The questionnaires completed by IG's wife reflected this decline (CDR-SOB 7.5, CBI-R 73), in particular highlighting significant problems with judgement, writing letters, using the telephone and electrical appliances and an increased predilection for sweet foods.

At his initial memory clinic appointment a diagnosis of frontotemporal dementia was made. In particular, the clinical features reported by IG and described by his wife are in keeping with the behavioural variant of this condition.

Case 5 (EX041) Posterior Cortical Atrophy Variant of Alzheimer's Disease (NCEE)

JB is 64-year old retired accountant. She initially presented to the memory clinic in July 2015 but no diagnosis was made at that time. She was seen again in February 2016, on which occasion a diagnosis of mild Alzheimer's disease was made. In August 2016 she was seen for a third time. At that appointment a diagnosis of the posterior cortical atrophy variant of Alzheimer's disease was made.

In 2015 she described a 2-year history of gradual cognitive decline. She reported struggling with complex tasks, to a degree that had prompted her early retirement. However, she recognised that her problems were often not noticeable to others. Her ACE-III score at that appointment was 74/100 and a CT head scan showed only mild involutional changes. The findings on a subsequent MRI scan were in keeping with a diagnosis of PCA.

At the time of her initial PrESIDe assessment in February 2017 (4 years after the reported onset of symptoms) she reported a range of cognitive impairments. By

her own admission, her memory was bad and getting worse. She struggled with complex sequences of tasks such as cooking or navigating routes. She had been attending French lessons and although she had always been academically very successful she now found herself unable to keep up with the rest of the class. Despite this she felt that she was still good with names and had good verbal communication. She reported that she had trouble telling the time from a clock, might struggle to see what was right in front of her and could fail to notice objects. Climbing stairs had become difficult, because she struggled to walk on uneven surfaces. On a recent holiday on a river cruise she had great difficulty in navigating the boat and on several occasions got lost finding her way back to the cabin.

At that time her ACE-III score was 72 (attention 13/18, memory 17/26, fluency 10/14, language 26/26, visuospatial 6/16). On the informant questionnaires the CDR-SOB was 4.0 and the total CBI-R score was 44. These questionnaires highlighted problems completing everyday tasks such as writing letters and using a telephone and a moderate difficulty in handling complex problems.

The ACE-III score had fallen further to 65/100 after 12-months (February 2018) (attention 13/18, memory 20/26, fluency 5/14, language 26/26, visuospatial 1/16). The informant questionnaires drew attention to the same problems but also reflected JB's own frustrations at her difficulties in self-care (including grooming and dressing) some mild problems in feeding herself, and worsening of her previously reported low mood. At that appointment the CDR-SOB had increased to 7.5 and the CBI-R to 51.

The pattern of cognitive impairments seen in JB - relatively preserved memory in the face of dramatic decline in visuospatial skills - alerted clinicians to the diagnosis of posterior cortical atrophy which was confirmed using established diagnostic criteria.

Case 6 (EX067) Mild Cognitive Impairment (NCEE)

DM is an 82-year old retired tax inspector. He presented to the memory clinic in June 2016 with a 2 year history of memory problems. He reported that he could

lose things now and again and his wife had noticed difficulty with remembering the names of people, and an occasional wrong turn when driving. There was however, no concern regarding the safety of his driving. DM felt that he was slower at processing information than he was before although he was still able to manage household finances without any assistance.

There were no concerns about behavioural or mood change, no problems with sleep and no evidence of psychosis or hallucinations of any form. At this appointment the ACE-III score was 92/100 (attention 18/18, memory 23/26, fluency 9/14, language 26/26, visuospatial 16/16). A CT head scan showed some age-related involutional changes but no significant abnormalities.

At his first PrESIDe assessment (March 2017), DM reported that his memory was working at 'about 50%' and 'getting gradually worse'. He denied ever getting lost, but was becoming increasingly reliant on writing down plans and appointments on a calendar in order to avoid forgetting them. His past medical history included atrial fibrillation, for which he takes warfarin. He reported a family history of dementia (Alzheimer's disease in his eldest sister). On that occasion his ACE-III score was 88/100 (attention 17/18, memory 22/26, fluency 8/14, language 25/26, visuospatial 16/16). The CDR-SOB was 2.0 and the CBI-R total score was 31. These questionnaires pointed towards difficulties in remembering names of people and objects and occasional problems with losing or misplacing things.

As he had been diagnosed with MCI at his memory clinic appointment, DM underwent further neuropsychological testing. On the Rey Auditory Verbal Learning Task (RAVLT) he reached the 80% criteria (12/15 words) after 9 trials, recalled 5 after interference and only 3 after 30 minutes. The Rey Complex Figure copy score was 32/36 but fell to 10/36 after 30 minutes. The time on the Trail Making Test A was 68 seconds, TMT B 189 seconds. These tests identified a degree of impairment in keeping with the MCI diagnosis, being greater than 1 standard deviation below age and education standardised normative data.

At his 12-month follow-up assessment (March 2018), the ACE-III score was 75/100 (attention 14/18, memory 14/26, fluency 7/14, language 26/26, visuospatial 14/16). This decline was also echoed by the CDR-SOB (6.5) and CBI-R (56) where difficulties in remembering what day it is, repetition, poor day-

to-day memory and concentration had all increased. DM himself denied significant decline in his memory function but his wife was aware that his memory problems had begun to affect what he could do and what he could not do. She had taken over management of the household finances and was no longer happy to let him go to the shops by himself, as when he did he would invariably forget certain items.

Given the decline in his cognitive and everyday functioning between the time of his initial memory clinic appointment and his 2nd PrESIDe assessment it was clear, based on diagnostic criteria, that DM had converted from MCI to AD over the course of the preceding 2 years.

Case 7 (EX001) Epilepsy Probable 1 (AD)

NM is a 88-year old who was seen alongside her daughter in the memory clinic in April 2016 with a 2-3 year history of progressive memory impairment. Whilst NM herself did not feel she had a significant problem, her daughter described a number of short term memory difficulties which had been becoming increasingly hard to miss. She was forgetting conversations and had trouble remembering recent events. She was now completely reliant on her daughter to remember appointments. There were reports of some word finding difficulties and navigational difficulties.

NM's daughter also reported occasional episodes of poor memory which is much worse than at other times. These often occur alongside brief periods of unresponsiveness where she appears to 'disappear off somewhere' and on some occasions makes repetitive movements in the arms and hands. Both her son and daughter had witnessed her making repeat picking movements with her right hand over the blanket on her lap in an almost trance-like state. These episodes were followed by a period of fatigue and increased confusion. Given this clear story of repeated, witnessed episodes which were suggestive non-convulsive seizures NM was characterised in to the epilepsy probable group. Her cognitive impairment met diagnostic criteria for Alzheimer's disease.

At her memory clinic appointment NM scored 78/100 on the ACE-III examination (attention 18/18, memory 18/26, fluency 6/14, language 20/26, visuospatial 16/16). By the time of her initial PrESIDe appointment (November 2016) this had decreased to 71/100 (attention 16/18, memory 15/26, fluency 8/14. Language 17/26, visuospatial 15/16). NM's daughter reported ongoing episodes of being vacant, but these had decreased in frequency following the initiation of Levetiracetam treatment (current dose 500mg twice daily). The CDR-SOB was 8.0 and the CBI-R 34. The questionnaires highlighted problems with poor day-to-day memory and becoming confused in unfamiliar surroundings.

At the 12-month follow-up assessment (December 2017) the ACE-III score had further declined to 63/100 (attention 16/18, memory 15/26, fluency 6/14, language 11/26, visuospatial 15/16). This was associated with relative stability in the CDR-SOB (7.5) and CBI-R (39). The CDR highlighted that NM was unable to make judgements or solve problems, and needed occasional prompting with personal care. NM now rarely left the house, except to go to bingo, and showed little interest in doing anything outside of her usual routine.

Case 8 (EX084) Epilepsy Probable 2 (MCI-AD)

KK is 75-year old retired naval officer who was seen in the memory clinic in July 2016 with a 1-2 year history of memory concerns. He was aware that he was forgetting details of conversations and could forget the names of people. He was increasingly reliant on writing things down to help him keep track of what was going on, and on a couple of occasions he failed to remember places he had visited before.

In March 2016 he had a single, witnessed, generalised tonic-clonic seizure. Following that seizure an MRI had been performed, which did not show any significant abnormalities. At the time of his memory clinic appointment his ACE-III score was 84/100 (attention 17/18, memory 17/26, fluency 8/14, language 26/26, visuospatial 16/16). Whilst the cognitive testing highlighted memory impairments, it was not felt that these had progressed to a degree that was limiting KK's ability to perform his day-to-day activities and consequently a diagnosis of MCI was made.

At the time of his initial PrESIDe appointment (April 2017) KK felt that there had been further cognitive decline. The ACE-III score was now 83/100 (attention 17/18, memory 18/26, fluency 9/16, language 24/26, visuospatial 15/16). The CDR-SOB score was 4.0 and the CBI-R score 51. The CDR highlighted moderate memory loss which interferes with everyday activities. Given the memory clinic diagnosis of MCI, further neuropsychological testing was performed. On RAVLT he reached the 80% criteria after 10 trials, recalled 4 after interference and only 3 after 30 minutes. The RCF copy score was 34/36, and fell to 18.5 after 30 minutes. TMT A was 62 seconds, TMT B 108 seconds. These memory tests highlight a cognitive impairment greater than 1.5 SD below age-matched normative data and alongside the memory impairment which was felt to be limiting daily activities KK met diagnostic criteria for a diagnosis of AD.

Between his memory clinic appointment and his baseline PrESIDe assessment KK had experienced no further tonic-clonic seizures but did report episodes of having a ‘muzzy’ head. He could seem vacant, and on occasion confused, take a long time to answer simple questions and struggling more than normal to remember information he was told. He would often sleep for several hours after these events. Given these episodes and the previous generalised seizure, KK was diagnosed with epilepsy and started on Levetiracetam (current dose 750mg twice daily).

By the time of his 12-month follow-up assessment (April 2018), the ACE-III score had further decreased to 72/100 (attention 13/18, memory 16/26, fluency 4/15, language 23/26, visuospatial 16/16). The CDR-SOB was 4.0 and the CBI-R 54, pointing towards moderate difficulty in handling complex problems, poor day-to-day memory constantly and frequently misplacing things around the house. Whilst there had been no further tonic-clonic seizures there had been further ‘strange’ episodes of acutely increased confusion, where KK could seem ‘puzzled’. On one occasion he went to let the dog out in to the garden, having completely forgotten that the dog had died almost 12-months ago, which was a mistake that he had not made before, or since.

Given these witnessed, recurrent episodes of abnormal behaviour and a previous tonic-clonic seizure, KK was categorised in to the epilepsy probable group.

Case 9 (EX005) Epilepsy Possible 1 (MCI-AD)

FM is an 84-year old retired builder. He was seen in the memory clinic, alongside his wife in August 2016. They had previously been seen there 2 years previously, at which point a diagnosis of MCI had been made. In 2016 FM reported that he had problems with forgetting less familiar names and faces, and short-term memory loss. It was felt that, despite these problems, FM remained independent and had no significant loss in efficiency or ability when completing everyday tasks. At that time he was still driving. His ACE-III score from the 2016 appointment was 79/100 (attention 18/18, memory 22/26, fluency 7/14, language 17/26, visuospatial 15/16). A CT head scan showed mild small vessel disease, as it had done in 2014. Overall there had been no significant functional decline since 2014 and the diagnosis of MCI was maintained.

In January 2017, FM underwent his initial PrESIDe assessment. He again reported that his short-term memory was 'not so good' and that he might forget the names of people he didn't know so well. He denied any problems with route-finding or navigation, and there was no history of mood or behaviour change, hallucination or psychosis. On further questioning FM's wife reported a single episode of unresponsiveness 6 months previously (between the memory clinic appointment and PrESIDe assessment). This episode lasted less than a minute, and was not convincingly followed by a period of confusion. There was no tongue-biting or urinary incontinence. On one further occasion FM's son had found him at home and reported that he was 'dazed' and 'a bit out of sorts' but no further information was available. At the time of his PrESIDe assessment FM's ACE-III score was 83/100 (attention 18/18, memory 24/26, fluency 6/14, language 20/26, visuospatial 15/16). The CDR-SOB score was 0.5 and the CBI-R 27. As a diagnosis of MCI was made at the memory clinic, further neuropsychological testing was performed. On RAVLT he reached the 80% criteria after 9 trials, recalled 5 after interference and only 2 after 30 minutes. The RCF copy score was 33/36, and fell to 10/36 after 30 minutes. TMT A was 51.67 seconds, TMT B 136 seconds. Although the ACE-III score had not deteriorated, the performance on these tests, alongside evidence of functional impairment on the history, meant that the diagnostic criteria for dementia were met at this time, changing the

diagnosis from MCI to AD. Given the single episode of witnessed unresponsiveness, and a further unclear episode of out-of-character confusion FM was classified into the epilepsy possible group.

At the time of the 12-month follow-up appointment (January 2018) there had been a decline in the ACE-III score to 70 (attention 17/18, memory 14/26, fluency 6/14, language 17/26, visuospatial 16/16). This change was accompanied by some increased concerns reported by FM's wife, of worsening short-term memory, poor recall of recent conversations, and some navigational problems. FM had now stopped driving. At this time the CDR-SOB was 2.5 and the CBI-R score was 38. These questionnaires identified an increased frequency in forgetting the names of familiar people, and poor concentration when reading or watching television. However, no further episodes of unresponsiveness were reported.

Case 10 (EX117) Epilepsy Possible 2 (AD)

SR, an 81-year old retired manager of an engineering company was seen alongside his wife in the memory clinic in February 2017. She reported a 1-year history of progressive memory problems affecting conversations, names, and misplacing items. His ACE-III score at that time was 70/100 (attention 16/18, memory 17/26, fluency 3/14, language 23/26, visuospatial 11/16). A CT head scan was performed and this reported age-related involutional changes and minimal small vessel ischaemic changes. Given the degree of memory impairment which was reported and the effect of this on SR's daily function, a diagnosis of AD was made and Donepezil was initiated.

By the time of the initial PrESIDe assessment (August 2017), there had been clear deterioration in his cognitive function, such that the ACE-III score had decreased to 60/100 (attention 15/18, memory 12/26, fluency 2/14, language 21/26, visuospatial 10/16). He met diagnostic criteria for AD. The CDR-SOB was 2.0 and the CBI-R score 27, describing mild consistent forgetfulness, moderate difficulty handling complex problems and losing or misplacing things on a roughly daily basis. SR's wife reported a few occasions where SR may appear briefly 'out of it'. At these times his head might drop and then afterwards he picks it up and carries on as he was before. These episodes remained unexplained and

investigations were ongoing to elucidate a possible cause. Unfortunately SR did not tolerate his Donepezil medication and this had therefore been stopped.

When he was reviewed in August 2018 for his 12-month follow-up PrESIDe assessment, the ACE-III score had decreased to 50/100 (attention 7/18, memory 10/26, fluency 2/14, language 19/26, visuospatial 12/16). The CDR-SOB was 7.0 and the CBI-R score was 68. These questionnaires now reported that SR was usually disorientated in time, often for place, was severely impaired in handling problems and had moderate memory loss. He was now reliant on his wife for his medication, appointments and all meals. Whilst a year ago she had been happy to let him walk in to the village by himself to buy a paper each day, she now made sure this was delivered to the house due to her concerns about his memory.

SR had had further brief vacant episodes, and his wife was concerned that on a couple of occasions he had seemed more confused than others, although the cause of these episodes remained incompletely understood. Whilst these episodes were repeated and stereotyped, it was not clear that they represented epileptic seizures, and as a result SR was classified as epilepsy possible.

APPENDIX 6: TIME DATA COLLECTION FORM

TIME Background History

Interviewer		Interview_date	
Place_of_interview			

First_name		DOB	
Last_name		Age_first_seen	

Witness		First_attack_date	
Initial_diagnosis		Last_attack_date	
Initial_diagnosis_date		Age_onset	
TEA_Diagnosis_date		First_to_last_attack	
Duration_epilepsy_months		(months)	

Total_number_attacks		Duration 1st attack	
Yearly_frequency_attacks			
Duration_of_attacks			

Seizure features. Please indicate Y or N

Attacks_on_waking	YES/ NO	Description of other seizure types
Triggers	YES/ NO	
Aura	YES/ NO	
Pure_amnesic_attacks	YES/ NO	
Automatisms	YES/ NO	
Olfactory_gustatory_hallucinations	YES/ NO	
Decreased_sense_smell	YES/ NO	
Dejavu	YES/ NO	
Period_of_unresponsiveness	YES/ NO	
Other_seizure_types	YES/ NO	
Repetitive_questioning	YES/ NO	
RNBATR	YES/ NO	

Seizure description

Degree_of_Ictal_AA	
Degree_of_Ictal_RA	
Postictal_state	
Subjective_during_attack	

Witness_during_attack	

Seizure details

Attack_example1	
Attack_example2	
Attack_example3	
Response_to_treatment	YES/ NO
Current_AEDs	
Previous_AEDs	
Current_other_medication	
EEG	YES/ NO
EEG_result	
MRI	YES/ NO
MRI _result	

Antibodies_test	YES/ NO
Antibodies_result	

Memory Disturbances

Accelerated_forgetting	YES/ NO		
ALF_details			
Autobiographical_RA	YES/ NO	Extent_autobiog_RA	
RA_details			
Public_event_amnesia_recent	YES/ NO		
Public_event_amnesia_remote	YES/ NO		
Topographical_amnesia	YES/ NO		
Names_faces_amnesia	YES/ NO		

Other changes

Pathological_emotionalism	YES/ NO
Current depression	YES/ NO
Current anxiety	YES/ NO

Medical History

Birth_history	YES/ NO
Birth_history_details	
Childhood_milestones	YES/ NO
Childhood_milestones_details	
Febrile_seizures	YES/ NO
Febrile_seizures_details	
Significant_head_injury	YES/ NO
Head_injury_details	

Intracranial_infection	YES/ NO
Intracranial_infection_details	
Migraine	YES/ NO
Migraine_details	
Stroke	YES/ NO
Stroke_details	
TIA	YES/ NO
TIA_details	
Hypertension	YES/ NO
Hypertension_details	
Ischaemic_HD	YES/ NO
Ischaemic_HD_details	
Other_cardiac	YES/ NO
Other_cardiac_details	
Peripheral_Vascular_Disease	YES/ NO
PVD_details	
Diabetes_mellitus	YES/ NO
Diabetes_mellitus_details	
Hyperlipidaemia	YES/ NO
Hyperlipidaemia_details	
Current_smoker	YES/ NO
Current_smoker_details	
Ex_smoker	YES/ NO
Ex_smoker_details	
Other_epilepsy_risk_factors	YES/ NO
Other_epilepsy_risk_factors_details	

Past_psychiatric_hx	YES/ NO
Past_psychiatric_hx_details	

Hx_of_Medically_Unexplained_Sx	YES/ NO
MUS_details	

Alcohol_excess	YES/ NO
Alcohol_details	

Recreational_drugs	YES/ NO
Recreational_drugs_details	

Past_medical_history	

Family medical history

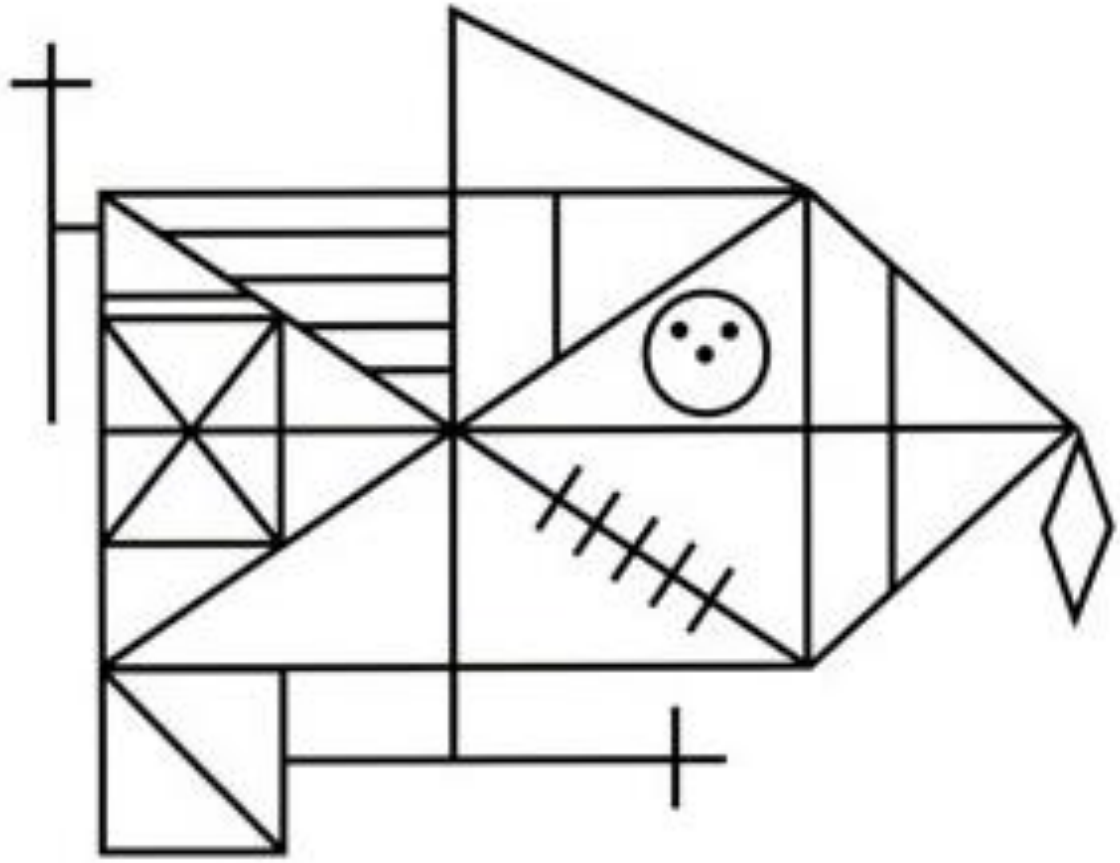
Family_history_epilepsy	YES/ NO
First_degree_family_history	YES/ NO
Details_of_Family_History	

Vascular_family_history	YES/ NO
Vascular_family_history_details	

Other_information	

Age left school
Years of education
Marriage status
Employment status

APPENDIX 7: REY-OSTERRIETH COMPLEX FIGURE



APPENDIX 8: REY AUDITORY VERBAL LEARNING TEST (RAVLT)

Trial 1 **- I am going to read a list of words. Listen carefully, for when I stop, you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can.** Read list 1, with a 1 sec interval between each word. Give no feedback.

Trial 2 – 10 - **Now I am going to read the same words again, and once again when I stop, I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before.**

After reached criterion: 12/15 or after 10 trials**: Please count backwards from 100** (stop after 40"). **Now what were those words I asked you to remember?**

After 30 mins **A short while ago I read a list of words to you several times, and you were trying** to learn these words. Tell me the words from that list again **(that is, the list that we went through several times).**
Start time:_____ End time: _____ Trials to criterion:

	Training												Recall Trials	
	1	2	3	4	5	6	7	8	9	10		Interf-40".	30'	3 days
Drum											Drum			
Curtain											Curtain			
Bell											Bell			
Coffee											Coffee			
School											School			
Parent											Parent			
Moon											Moon			
Garden											Garden			
Hat											Hat			
Farmer											Farmer			
Nose											Nose			
Turkey											Turkey			
Colour											Colour			
House											House			
River											River			
SCORE														

APPENDIX 9: HOSPITAL ANXIETY AND DEPRESSION SCALE

For each of the following 14 statements, please circle the number (0,1,2,3) that most accurately corresponds to how you currently feel.

1	**I feel tense or 'wound up':**	A
	Most of the time……	3
	A lot of the time ……	2
	From time to time, occasionally ……	1
	Not at all ……	0
2	**I still enjoy the things I used to enjoy:**	D
	Definitely as much ……	0
	Not quite so much ……	1
	Only a little ……	2
	Hardly at all ……	3
3	**I get a sort of frightened feeling as if something awful is about to happen:**	A
	Very definitely and quite badly ……	3
	Yes, but not too badly ……	2
	A little, but it doesn't worry me ……	1
	Not at all ……	0
4	**I can laugh and see the funny side of things:**	D
	As much as I always could ……	0
	Not quite so much now ……	1
	Definitely not so much now ……	2
	Not at all ……	3
5	**Worrying thoughts go through my mind:**	A
	A great deal of the time ……	3
	A lot of the time ……	2

From time to time, but not too often 1

Only occasionally 0

6 **I feel cheerful:** D

Not at all 3

Not often 2

Sometimes 1

Most of the time 0

7 **I can sit at ease and feel relaxed:** A

Definitely 0

Usually 1

Not often 2

Not at all 3

8 **I feel as if I am slowed down:** D

Nearly all the time 3

Very often 2

Sometimes 1

Not at all 0

9 **I get a sort of frightened feeling like 'butterflies' in the stomach:** A

Not at all 0

Occasionally 1

Quite often 2

Very often 3

10 **I have lost interest in my appearance** D

Definitely 3

I don't take as much care as I should..... 2

I may not take quite as much care 1

I take just as much care as ever 0

11 **I feel restless as I have to be on the move:** A

Very much indeed 3

Quite a lot 2

Not very much 1

Not at all 0

12 **I look forward with enjoyment to things:** D

As much as I ever did 0

Rather less than I used to 1

Definitely less than I used to 2

Hardly at all 3

13 **I get sudden feelings of panic:** A

Very often indeed 3

Quite often 2

Not very often 1

Not at all 0

14 I can enjoy a good book or radio or TV program: D

Often 0

Sometimes 1

Not often 2

Very seldom 3

Total A:

Total D:

0-7	N
8-10	B A
11-21	A

APPENDIX 10: AN ILLUSTRATIVE CASE FROM THE TIME STUDY

Case VA (case ID 195)

In 2013, a 59yr right handed aircraft engineer, VA, was referred to the cognitive neurology clinic. He described a two-year history of transient episodes of memory impairment.

The first of these occurred whilst on a motorcycle holiday with his wife. One morning, he woke up, unsure of where he was or what he had been doing on the previous day. He did not ask repetitive questions and within a few minutes he had returned to normal. As they were in the middle of their holiday his wife attributed his disorientation to their travels and thought nothing more of it. VA himself does not recall this episode.

Approximately one month later, VA awoke unsure of where he was. He was unable to recollect his son's wedding which had taken place 4 days previously. Once again, this lasted for only a few minutes before resolving. His amnesia for this episode was incomplete: he is able to remember not being able to remember.

One month after that, a further episode occurred whilst visiting his daughter in her new house. VA's wife reports that she saw him walking to the bedroom window and asking 'where are we?' He could not recall the previous day, or that they were staying with their daughter.

At around this time VA's wife noticed that these early morning amnesic episodes would be preceded by 'mouthing movements'. VA himself would notice a strange taste or smell, which was sometimes pleasant and sometimes unpleasant, at the time of these episodes.

In addition to these transient episodes of memory impairment, VA reported some interictal memory disturbances. He described 'blanks' for salient events over the last 5 years. These included holidays, weddings and other events which he felt that he should have been able to remember. He felt that memories 'faded' more rapidly than he would have expected. For example, if he was to read a book, he could pick it up again a week later, with no recollection that he had read it before. Although he reported that his memory for routes had never been particularly

good, he was also aware that this had deteriorated over the same period. In particular he found it difficult to visualise familiar routes.

He described being more emotional than he was previously; he could be moved more easily by something on radio or television. Furthermore, he reported that he was more irritable than he had been prior to the start of these episodes.

His past medical history is notable only for previous sinus surgery which had affected his sense of smell, and two episodes of what he referred to as 'burn-out' in 1989 and 1999. Although, he has never satisfied the criteria for major depression, he met criteria for current and past generalised anxiety disorder. He is a non-smoker, with no history of excess alcohol consumption.

His neurological examination was entirely normal as was an MRI brain scan. An EEG showed occasional bursts of low voltage discrete spike and slow wave activity maximal over the right centro-temporal region. An example of this abnormality is shown below (fig.1). Given the clinical history, and evidence provided by the EEG, it was felt that VA's amnesic events were epileptic seizures. VA was started on lamotrigine which was increased up to 100mg. He has had no further episodes since commencing treatment in December 2013.

Following his initial interview VA was recruited to the TIME (The Impairment of Memory in Epilepsy) study, and underwent a formal neuropsychological evaluation. The battery comprised standard tasks to estimate premorbid and current general cognitive ability, visual and verbal anterograde memory tests, a semantic memory test, and tests of executive function. Episodic autobiographical memory across the life span was assessed via the Modified Autobiographical Memory Interview. Finally, to assess forgetting over time, VA completed a modified version of a word learning task, the Rey Auditory Verbal Learning Test (RAVLT). Here he was required to repeat learning trials until he could recall at least 80% (12 words) of the list, with delayed recall assessed at 30 minutes and at 1 week.

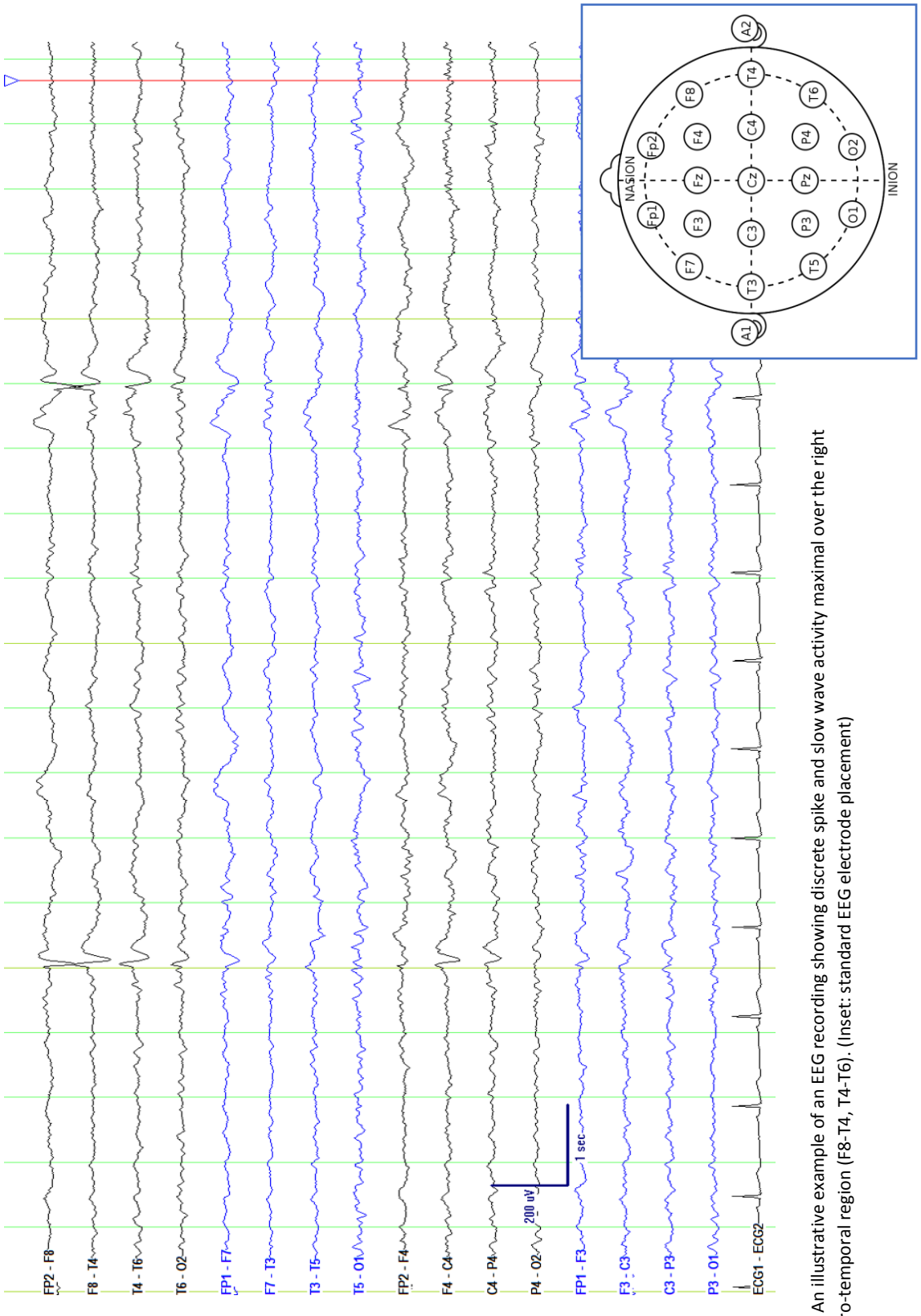


Fig1. An illustrative example of an EEG recording showing discrete spike and slow wave activity maximal over the right centro-temporal region (F8-T4, T4-T6). (Inset: standard EEG electrode placement)

Overall, VA's general cognitive abilities were rated within the high average range for his age. There was no evidence of impairment in his visuo-constructional abilities, executive function or semantic memory (although his approach to drawing the Rey Complex Figure task was somewhat unusual and fragmented). He performed variably on tests of anterograde memory. He showed good verbal recognition memory (words), and his learning over the standard 5 trials of the RAVLT was within the average range for his age. He was, however, less efficient in reaching the 80% learning criterion when compared with IQ-matched healthy controls, but did well to maintain his learning after a 30-minute delay. VA's immediate recall of a story was low average, while his 30 minute recall was poor. Visual memory was generally weaker. He showed disproportionally poorer visual recognition (for faces versus words) to a level observed in only 5-10% of his peer group. His recall of the complex figure was distorted and below the 1st percentile for his age.

When retention of information was assessed over a longer period (1 week), clear difficulties emerged. VA was unable to freely recall any of the words correctly from the list (recalling he had done the task, but confabulating 4 incorrect responses). Although he correctly recognised 13 of the 15 words when cued, he also endorsed having learned 5 words that were not on the list.

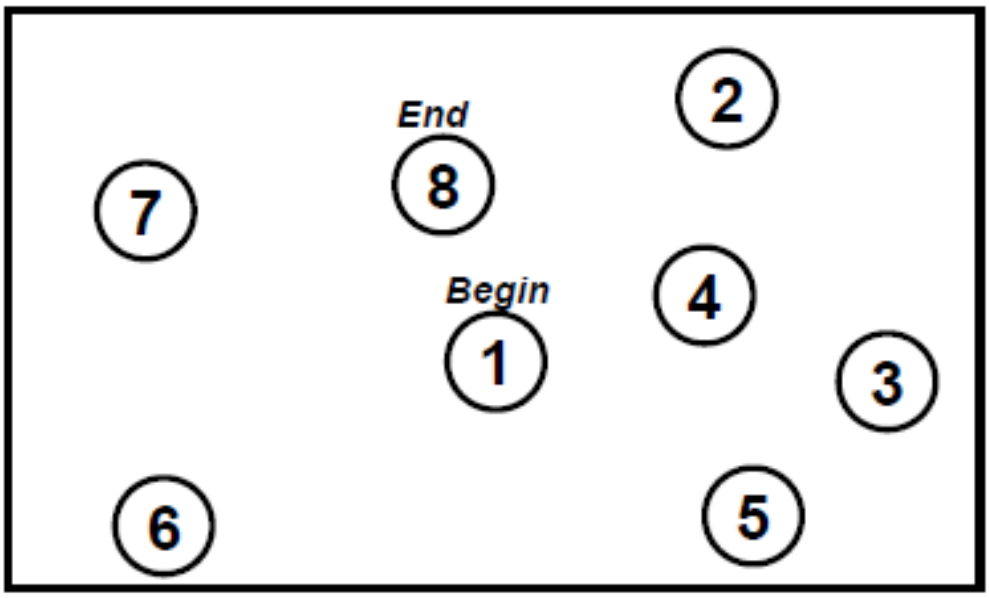
Assessment of his autobiographic memory revealed that while VA could recall specific events from each of the decades of his life, these often lacked rich episodic detail. In one instance, he could recall facts regarding his son's wedding which he attended in 2005, but was unable to describe any part of the event.

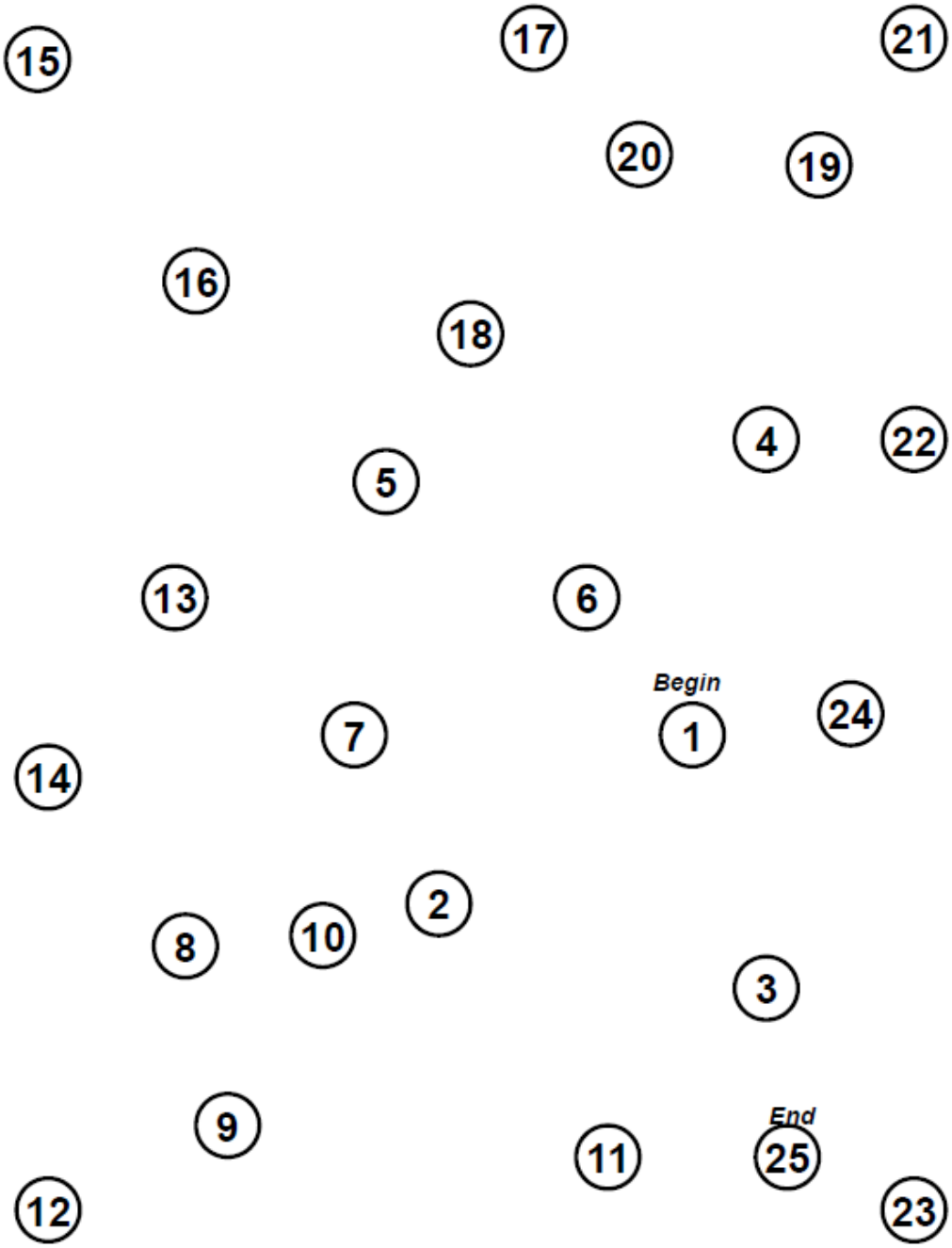
APPENDIX 11: TRAIL MAKING TEST VERSIONS A AND B

TRAIL MAKING

Part A

SAMPLE

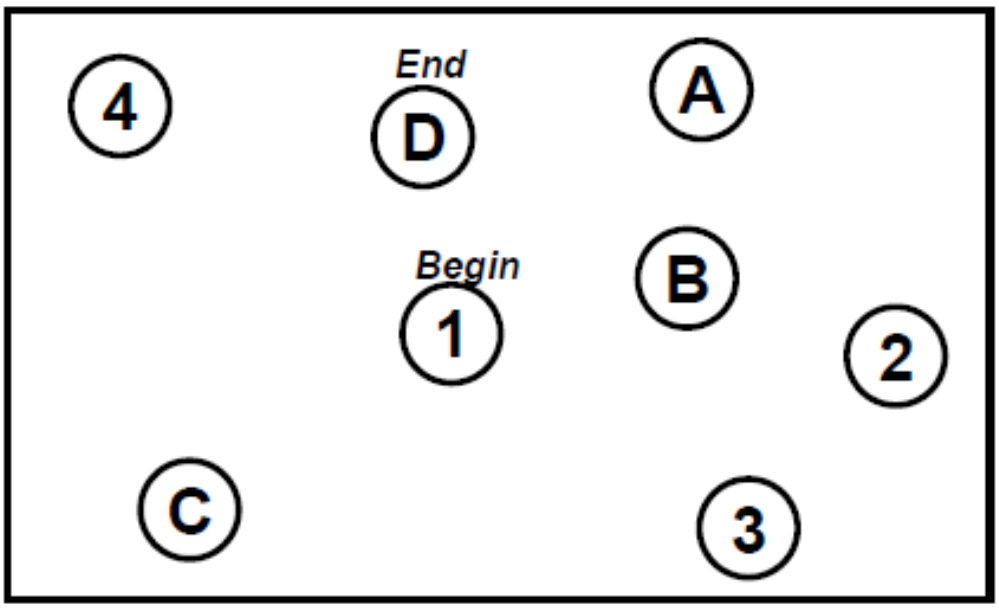


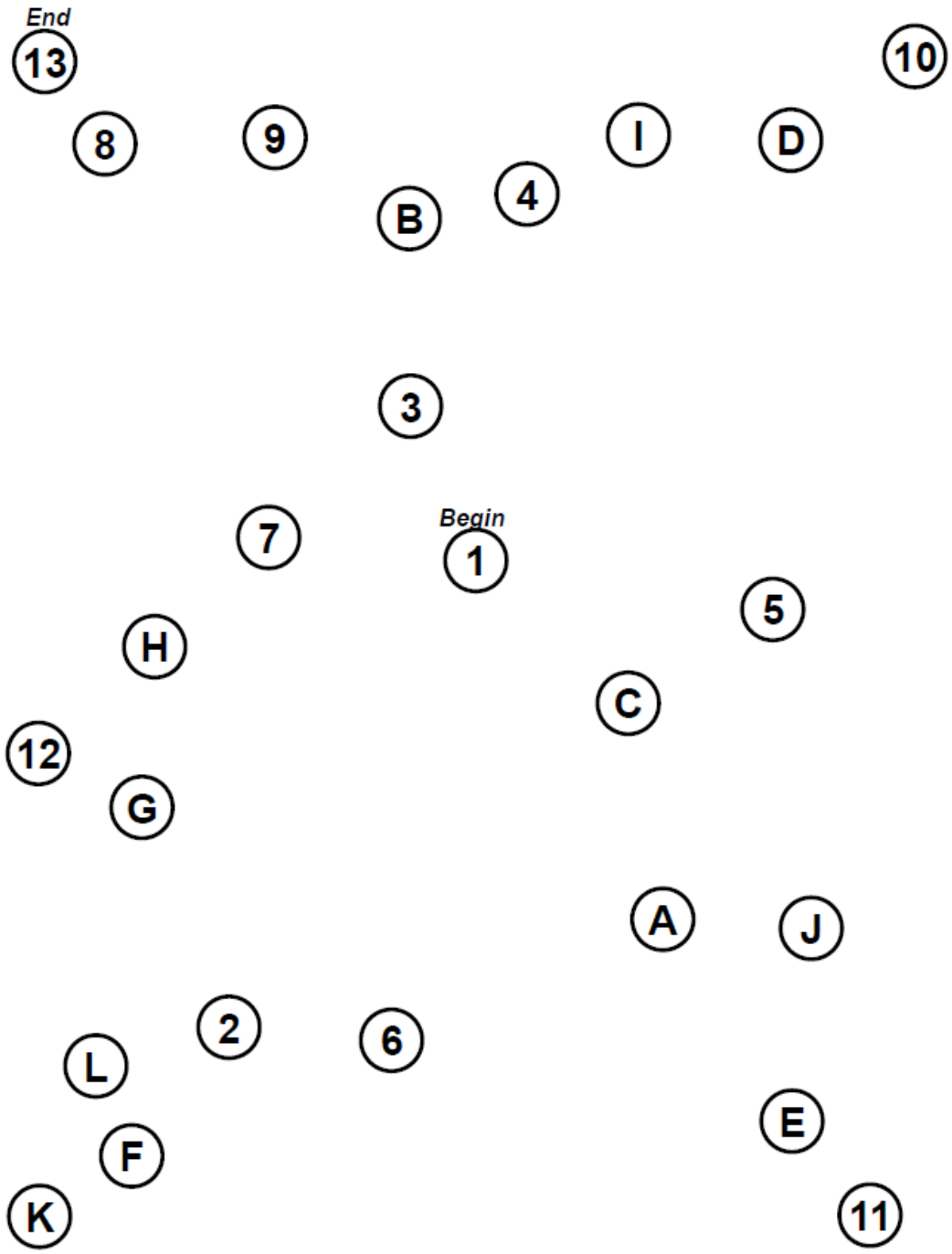

15
17
21
20
19
16
18
4
22
5
13
6
Begin
24
7
1
14
2
8
10
3
9
End
11
25
12
23

TRAIL MAKING

Part B

SAMPLE




End
13
10
8
9
I
D
4
B
3
7
Begin
1
5
H
C
12
G
A
J
2
6
L
E
F
K
11

APPENDIX 12: DIGIT SPAN TEST

Digit Span (WMS-III)

"I am going to say some numbers. Listen carefully, and when I am through, I want you to say them right after me. Just say what I say." Discontinue after two consecutive errors on the same item number.

Forwards

Item	Trial	Response	Score 0 or 1
1	1-7		
	6-3		
2	5-8-2		
	6-9-4		
3	6-4-3-9		
	7-2-8-6		
4	4-2-7-3-1		
	7-5-8-3-6		
5	6-1-9-4-7-3		
	3-9-2-4-8-7		
6	5-9-1-7-4-2-8		
	4-1-7-9-3-8-6		
7	5-8-1-9-2-6-4-7		
	3-8-2-9-5-1-7-4		
8	2-7-5-8-6-2-5-8-4		
	7-1-3-9-4-2-5-6-8		

Raw: _____ **Max Digits Forwards:**

"Now I am going to say some more numbers. But this time when I stop, I want you to say them backward. For example, if I say 7-1-9, what would you say?"
If correct: "That's right".
If incorrect: "No you would say 9-1-7. I said 7-1-9, so to say it backward you would say 9-1-7. Now try these numbers. Remember, you are to say them backward: 3-4-8."

Backwards

Item	Trial	Correct Response	Participant Response	Score 0 or 1
1	2-4	4-2		
	5-7	7-5		
2	6-2-9	9-2-6		
	4-1-5	5-1-4		
3	3-2-7-9	9-7-2-3		
	4-9-6-8	8-6-9-4		
4	1-5-2-8-6	6-8-2-5-1		
	6-1-8-4-3	3-4-8-1-6		
5	5-3-9-4-1-8	8-1-4-9-3-5		
	7-2-4-8-5-6	6-5-8-4-2-7		
6	8-1-2-9-3-6-5	5-6-3-9-2-1-8		
	4-7-3-9-1-2-8	8-2-1-9-3-7-4		
7	9-4-3-7-6-2-5-8	8-5-2-6-7-3-4-9		
	7-2-8-1-9-6-5-3	3-4-6-9-1-8-2-7		

Raw: _____ **Max Digits Backwards:**

_____

Total Raw: _____

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PRESENTATIONS AND PRIZES RESULTING FROM THE WORK PRESENTED IN THIS THESIS

Publications

Baker, J., Libretto, T., Henley, W. & Zeman, A. (2019). The prevalence and clinical features of epileptic seizures in a memory clinic population. *Seizure,* 71**,** 83-92

(This paper is reproduced as chapter 3 of this thesis)

Baker, J., & Zeman, A. (2017). Accelerated long-term forgetting in epilepsy—And beyond. In N. Axmacher & B. Rasch (Eds.), *Studies in neuroscience, psychology and behavioral economics. Cognitive neuroscience of memory consolidation* (pp. 401-417) Springer

(This chapter is reproduced in part as chapter 6 of this thesis)

Baker, J., Savage, S. & Zeman, A. (2019). VA: A case report of Transient Epileptic Amnesia. In S. E. MacPherson & S. Della Sala (Eds.), Cases of Amnesia: Contributions to Understanding Memory and the Brain (pp.240-260) Routledge

(This chapter is reproduced in part as appendix 10 of this thesis)

Baker, J., Savage, S. & Zeman, A. (2019). Cognitive Assessment. In R. Butler & C. Katona (Eds.), Seminars in Old Age Psychiatry (pp.27-40) Cambridge

Platform Presentations

'The Presentation of Epileptic Seizures in Dementia' SWENA 2019 (2nd Place prize)

‘Epileptic seizures in the memory clinic population: What are they like? Who is having them? When do they occur?’ Alzheimer’s Society Annual Conference 2018

‘The Prevalence and Clinical Features of Epileptic Seizures in the Memory Clinic Population’ University of Exeter Annual Research Event 2018

‘TIME2: consolidating the Transient Epileptic Amnesia phenotype’ GW4 Early Career Neuroscientist Day 2017

Poster Presentations

‘Epileptic Seizures in Alzheimer’s Disease: The PrESIDe study’ AAIC 2018, Chicago

‘The PrESIDe study: Investigating the prevalence of epileptic seizures in dementia’ ILAE 2018, London

‘Distinguishing Transient Epileptic Amnesia from Epilepsy in Dementia’ ABN 2018, Birmingham

‘The Prevalence and Clinical Features of Epileptic Seizures in the Memory Clinic Population’ Epilepsy Brain and Mind 2018, Brno (winner of poster prize)

‘The Presentation of Epileptic Seizures in Dementia: Findings of the PrESIDe study’ ARUK 2018, London

‘TIME2: a replication study of transient epileptic amnesia’ ABN 2017