SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

ACCELERATED LONG-TERM FORGETTING AND AUTOBIOGRAPHICAL AMNESIA IN TEMPORAL LOBE EPILEPSY

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By

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DECLARATION

I, Dr. Pavan Kumar Rudrabhatla, hereby declare that this project titled 'Accelerated long-term forgetting and autobiographical amnesia in temporal lobe epilepsy', was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

P. Pavan Kumar

28/8/20

Thiruvananthapuram,
Date: 28-08-2020.

Dr. Pavan Kumar Rudrabhatla

Forwarded:

The candidate, Dr. Pavan Kumar Rudrabhatla, has completed the project titled 'Accelerated long-term forgetting and autobiographical amnesia in temporal lobe epilepsy' under my guidance.

Thiruvananthapuram,
Date: 28-08-2020.

Dr. Sanjeev V. Thomas,
Professor (Senior Grade) and Head,
Department of Neurology,
SCTIMST.

Forwarded:

The candidate, Dr. Pavan Kumar Rudrabhatla, has carried out the project titled 'Accelerated long-term forgetting and autobiographical amnesia in temporal lobe epilepsy' as part of the minimum required project.

Thiruvananthapuram,
Date: 28-08-2020.

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Dr. Pavan Kumar Rudrabhatla

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SYNOPSIS

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Memory complaints of patients with Temporal Lobe Epilepsy (TLE), sometimes mismatch with the routine neuropsychological assessment. Novel forms of long-term memory (LTM) dysfunction, namely, accelerated long-term forgetting (ALF) and autobiographical amnesia (AA) have been described in TLE. Routine memory assessment at short duration intervals fail to identify these entities, often mislabeling the complaints as functional. We studied the memory dysfunction in 31 TLE patients using special tests, including delayed memory assessment at 5 days and Autobiographical Memory Interview (AMI) and comparing with healthy age/education matched controls.

Our study generated data on special tests of memory assessment in TLE. Patients with TLE showed a trend for accelerated log-term forgetting of verbal memory compared to controls. They also had significant autobiographical amnesia (both personal semantic domain and autobiographical incidents) for early adult life and recent life compared to controls. This dysfunction was observed both in right and left TLE. Our study did not find significant association between duration of epilepsy, recent seizure frequency, seizures during assessment period, antiepileptic drugs, and the outcome measures.

The data from our study can help in standardising protocols to assess memory dysfunction in persons with epilepsy (PWE) and in further research. As ALF and AA have disabling implications on quality of life, early identification is necessary for planning intervention strategies.

INTRODUCTION

INTRODUCTION

Epilepsy is a chronic neurological disorder with diverse etiology and clinical manifestations. The conceptual definition is that Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. As per International League Against Epilepsy (ILAE), (2014) operational definition, epilepsy refers to at least two unprovoked (or reflex) seizures occurring >24 hours apart or one unprovoked (or reflex) seizure with a probability of further seizures similar to general recurrence risk (at least 60%) after two unprovoked seizures, occurring over next 10 years [1]. Epilepsy affects people of all ages and both sexes. It is estimated that there are more than 10 million persons with epilepsy (PWE) in India [2]. The prevalence is higher in the rural (1.9%) compared to urban population (0.6%) [3].

Memory is defined as the mental faculty of retaining and retrieving facts, events impressions etc. In physiological terms memory has three stages: encoding, storage, and retrieval. Hippocampus plays an important role in encoding. In temporal lobe epilepsy (TLE) there is sclerosis and damage to the hippocampus that could interfere with its ability to encode memory. As a result, there can be difficulties in generating short-term and long-term memories or forward learning. The magnitude of memory dysfunction in epilepsy varies according to the study population and diagnostic methodologies. In one study 54% of over 700 people with epilepsy reported difficulties with memory as a moderate to severe problem [4]. Memory dysfunction can have important bearing on the quality of life of PWE.

Long-term memory (LTM):

Repetitive and simultaneous activation of two neurons leads to strengthening of the synaptic connection between them. This procedure is called Long-term potentiation (LTP),

which is the physiological basis for LTM [5]. LTM can be declarative (includes semantic and episodic memory) or non-declarative (includes procedural memory). Consolidation from short-term to long-term memory, happens primarily in the hippocampus and stored throughout the cortex [6]. It is well recognized that TLE may cause deficits on neuropsychological tests of memory, which typically assess the ability to retain new information over a delay of about 30 min [7]. But, sometimes the memory complaints of these patients do not match with the assessment at short intervals such as 30 minutes, so that complaints about memory decline commonly mismatch with test performance [8].

Transient Epileptic Amnesia (TEA) is a distinctive syndrome of temporal lobe epilepsy, causing brief, recurrent attacks of amnesia, often occurring on waking, generally in middle aged and elderly people. TEA patients were found to have novel forms of interictal memory disturbance: accelerated long-term forgetting (ALF), remote memory impairment, especially affecting autobiographical memory and topographical memory impairment [9,10,11]. Similar memory dysfunction has also been noted in patients in TLE. Various mechanisms have been proposed for ALF and autobiographical amnesia (AA), but still the exact underlying mechanism remains elusive.

Limitations of memory assessment in epilepsy:

Although it is widely held that people with epilepsy can have considerable memory dysfunction, the precise profile of the memory problem in epilepsy is yet to be completed. Conventional memory assessment may fail to identify memory dysfunction characterized by intact recall for a relatively brief period but rapid forgetting thereafter. Tests that estimate the memory function over standard intervals of minute to hours are too short to detect impaired long-term memory. It is difficult to draw firm conclusions from standard neuropsychological test alone as to whether patients are already impaired during encoding or if they just fail to

retrieve learned information. It is important to consideration the existence of inter-individual differences with respect to the type of impairment, such as, encoding or retrieval, recall or recognition, within the specific pathologies. Special test batteries are needed for the detection and assessing the severity of long-term memory dysfunction such as accelerated long-term forgetting and autobiographical amnesia.

Our study attempts to assess the memory function of patients with TLE using special test batteries. We also compare this data with age and Intelligence Quotient (IQ) matched healthy controls. We hope that this study would generate the baseline data for these test batteries in our subset of population and data on the magnitude of ALF/AA in TLE patients. We would be able to establish standardized protocols to estimate the memory dysfunction in people with epilepsy. The identification of this memory dysfunction can help in initiation of early intervention to improve quality of life in PWE.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Epilepsy and memory:

Epilepsy affects around 50 million people worldwide with estimated proportion of general population with active epilepsy being 4-10 per 1000 population. As per World Health Organization, around five million people are diagnosed with epilepsy globally each year. The magnitude of memory dysfunction in epilepsy varies according to the study population and diagnostic methodologies. In one study 54% of over 700 people with epilepsy reported difficulties with memory as a moderate to severe problem [4].

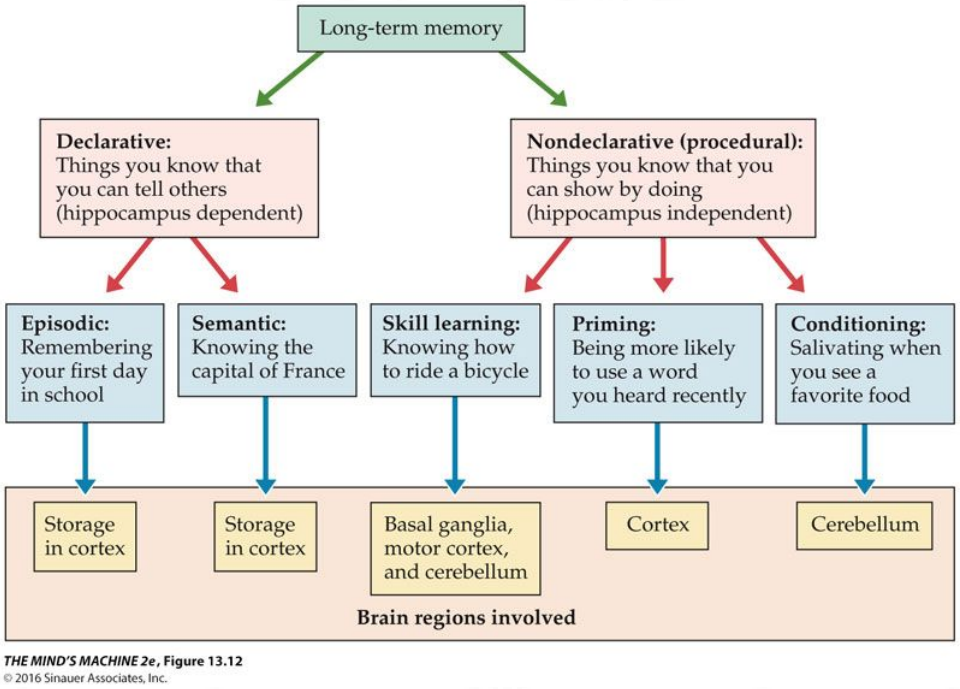
Memory dysfunction can have important bearing on the quality of life of PWE. In a study about 40% of the PWE with depression or other mood disturbances had significant short-term memory difficulty [12]. Short-term memory difficulty had been found to be associated with mood disorders in epilepsy [13,14,15]. In general, people with epilepsy and memory problems have a negative impact on daily life.

TLE and memory dysfunction:

It is well recognized that TLE causes memory dysfunction, and studies have shown these defects by neuropsychological tests, which typically assess the ability to retain new information over a delay of about 30 minutes [7]. The degree of impairment has been shown to correlate with pathological abnormalities [16,17,18], hippocampal atrophy [19,20,21] and other factors like the age of onset of epilepsy, seizure frequency and lifetime number of seizures [22,23,24,25,26]. The laterality of the seizure focus has consistently been found to influence the type of material for which memory is most affected, with left TLE causing more pronounced deficits in verbal memory, and, less consistently, right TLE affecting non-verbal memory [7,27,28].

Consolidation from short-term to long-term memory (LTM), happens primarily in the hippocampus and stored throughout the cortex [6]. LTM can be declarative (includes semantic and episodic memory) or non-declarative (includes procedural memory).

Figure 1: Types of long-term memory and brain regions involved



Hippocampus is a bilaminar gray matter structure located medially in the temporal lobe and plays an important role in the physiology of memory. It has two interlocking gray matter folds, hippocampus proper (cornu ammonis) and the dentate gyrus. The cornu ammonis is divided into four parts, (CA1 to CA4) based on cellular composition, called the Sommer's sectors. The hippocampus can be affected by a wide range of congenital variants and degenerative, inflammatory, vascular, tumoral and toxic-metabolic pathologies. The most common cause of medically intractable partial complex epilepsy in adults is mesial temporal sclerosis (MTS), which is characterized pathologically by hippocampal gliosis and neuronal loss. The cause of which is hypothesised to be early or prolonged febrile seizures [29].

Figure 2: Anatomical components of hippocampus on MRI (coronal section)[29]

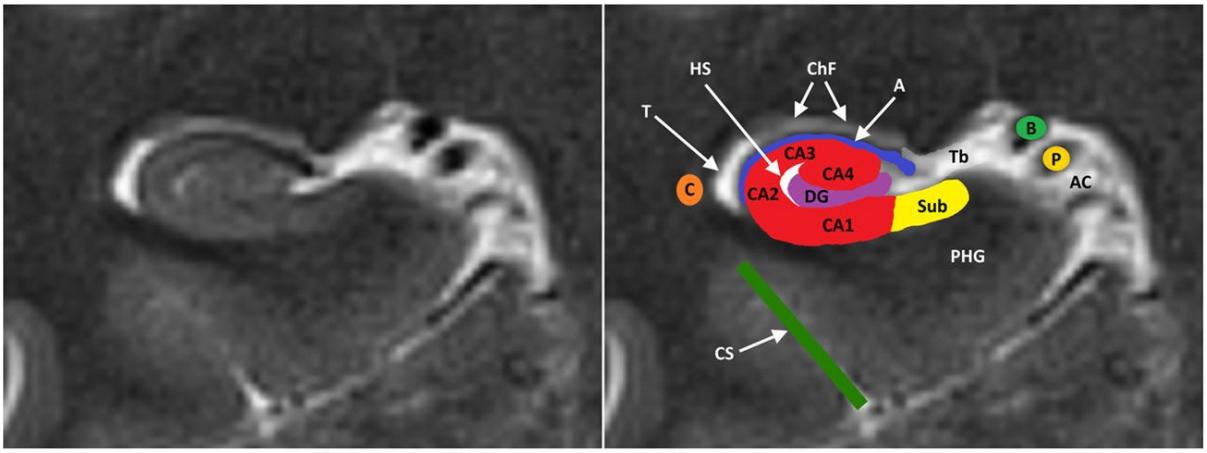
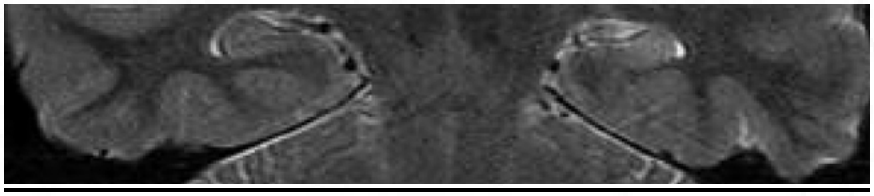


Figure 3: Left mesial temporal sclerosis (MTS) on MRI (coronal section)[29]



The severity of memory difficulty reported by some patients with TLE, correlates poorly with objective measures, and many patients perform at average or above-average levels on routine neuropsychiatric tests [30]. Studies on TLE (especially on Transient Epileptic Amnesia (TEA)) have identified novel forms of long-term memory dysfunction.

TEA and novel entities of memory dysfunction:

Transient Epileptic Amnesia (TEA) is a distinctive syndrome of temporal lobe epilepsy, causing brief, recurrent attacks of amnesia, often occurring on waking, generally in middle aged and elderly people. The characteristic features of patients with TEA and their performance in memory tests, using special test batteries have been analyzed in various studies [9,10,11]. It is associated with novel forms of interictal memory disturbance: accelerated long-term forgetting, remote memory impairment, especially affecting autobiographical memory and topographical memory impairment. The correlation between the subjective memory complaints

and objective testing on standard neuropsychological tests has generally been poor in all patients with TLE.

Two distinctive entities characterized by long-term memory deficits have been identified in patients with TLE:

(1) Accelerated long term forgetting - (ALF) is the rapid loss of newly acquired memories over days to week despite normal retention at standard (~30 min) intervals. It has recently been described in association with epilepsy, particularly the syndrome of transient epileptic amnesia (TEA). It is not uncommon for patients with ALF to have forgotten all the original material when their memory is tested at longer delays. It is also known that everyday memory complaints are more highly correlated with very long-term recall performance (that is, 24 hours or more) than they are with scores obtained on standard memory measures (with recall within 30 minutes) [9,31]. The mechanism underlying ALF remain uncertain.

(2) Autobiographical amnesia – (AA) Autobiographical memory refers to a multifaceted concept encompassing different kinds of knowledge, from general knowledge about oneself (semantic component) to specific personal events related to the self (episodic component) [32,33,34]. Autobiographical amnesia refers to large ‘‘gaps’’ in their more remote autobiographical memory; these commonly become apparent when discussing family events and holidays, of which they have no recall. Medial temporal lobe structures, such as the hippocampus, are known to play an important role in autobiographical memory [35,36]. In patients with hippocampal damage, the recollection of personal episodes is impaired [37,38,39,40]. The hippocampus and other mesial temporal lobe structures form an important part of the ABM retrieval network [36,41].

Research has also shown association between epilepsy and Alzheimer’s disease (AD). Studies have proposed that early development of occult hippocampal hyperexcitability may

contribute to the pathogenesis of AD [42]. Further research is needed to delineate the association of epilepsy, long-term memory dysfunction and Alzheimer's disease.

Drawbacks of conventional memory assessment:

Conventional memory tests which assess memory recall after minutes to hours, may fail to identify memory dysfunction characterized by intact recall for a relatively brief period but rapid forgetting thereafter. In many cases long-term memory impairments are not detected by standard neuropsychological test of memory functions, so that complaints about memory decline commonly mismatch with test performance [8].

Early literature on ALF in TLE:

The concept of long-term forgetting in temporal lobe dysfunction was studied since the late 20th century. Martin et al, 1991, investigated delayed recall performance in 21 patients with unilateral temporal lobe dysfunction which showed increased forgetting of verbal information at 24 hours compared to controls after a normal performance at 30 minutes. The need for memory assessment at further delayed intervals was stressed upon in this study [43]. A case report, 1997, of a medial temporal epilepsy after paraneoplastic limbic encephalitis, was one of the earliest descriptions of ALF in TLE [44]. They have described a normal retention of information for hours to days with absolutely no recall afterwards.

Kapur et al, 1997, described similar memory dysfunction in TLE and proposed a multi-stage process of memory consolidation [45]. Blake et al, 2000, is a prospective study of 23 patients, has shown that patients with left TLE had ALF (at 8 weeks assessment) for verbal material compared to patients with right TLE and controls after normal learning at 30 minutes [46].

There were some studies which did not demonstrate ALF in patients with TLE [47,48,49,50]. Bell et al, 2006, was one of such studies, in which, 25 cases of TLE and the same numbers of controls were studied [48]. TLE patients did not demonstrate disproportionate forgetting over two weeks when compared to controls after a comparable learning and recall at baseline and 30 minutes, respectively.

Mameniskiene et al, 2006, evaluated delayed and long-term (4 weeks) recall in 70 patients with TLE and 59 controls [51]. High frequency of seizures during the study period were related to poor long-term recall. Patients with complex partial and/or secondary generalized seizures had poor long-term recall compared to patients with simple partial seizures. The presence of interictal generalized or focal temporal epileptiform activity was associated with more accelerated forgetting of verbal and visual memory. Multiple regression analysis showed that number of complex partial seizures, age of patient, and abnormal interictal EEG are significant predictors of accelerated forgetting. Wilkinson et al, 2012, showed ALF in patients with TLE compared to controls both for verbal and visual memory [52].

Early literature on AA in TLE:

Studies on AA in TLE were conducted since the last decade of 20th century and they have confirmed the occurrence of AA in TLE, but they differed in the precise nature. Zeman et al, 1998, studies 10 patients with TEA and found significant deficits in autobiographical memory and proposed that it might have resulted from impairment of very long-term memory consolidation because of epileptic activity in mesial temporal structures [8]. Some studies have revealed an impairment of autobiographical memory throughout the entire life span [39,53], whereas in others the deficit extends back as little as 5 years [45].

Viskontas et al, 2000, assessed ABM in 25 patients with unilateral TLE and 22 non-neurologically impaired controls using the Autobiographical Memory Interview [33,39].

Results indicate that patients have impaired personal episodic memory extending over the entire lifespan but intact personal semantic memory. No significant difference in memory impairment was noted between patients with and without hippocampal sclerosis on imaging. These results indicate that even minimal damage to medial temporal lobes can result in significant impairment to autobiographical episodic memory or the involvement of extensive memory networks [33].

Some other studies have reported deficits in both autobiographical memory and semantic memory for public events with intact personal semantic memory [54,55]. Voltzenlogel et al, 2006, showed that both right and left TLE patients had impaired memory for autobiographic episodes and public events. In contrast, personal semantic memory was preserved. Right TLE patients had significantly better scores than left in the assessment. Duration of epilepsy, age at onset, and seizure frequency did not influence performance on remote memory measures [55]. Disproportionate loss of public semantics compared to autobiographical memory was noted in Barr et al, 1990; and Manning et al, 2005 [56,57]. This differential involvement of various components of remote memory noted in different studies would suggest that there is at least partial independence between these processes.

Recent evidence for both ALF and AA in TLE:

Manes et al, 2005, has studied 7 patients with TEA and 7 age-matched controls for both ALF and AA. Patients showed ALF of verbal material, with virtually no recall after 6 weeks. There was also an impaired recall of autobiographical memories in patients with TEA [11].

The TIME (The Impairment of Memory in Epilepsy) Study (Butler et al, 2007), recruited 50 patients with TEA and found significantly increased ALF and AA in cases compared to (age and education-matched) healthy controls [9]. A later study (Butler et al, 2009) of the same cohort, has analysed the imaging data of the patients and 20 matched healthy

controls, using manual volumetry and voxel-based morphometry (VBM). They studied the correlation between regional brain volumes, clinical and neuropsychological data. Manual volumetry identified subtle hippocampal volume loss in the TEA group. Both manual volumetry and VBM revealed correlations between medial temporal lobe atrophy and standard anterograde memory scores, but no relation between atrophy and ALF or remote autobiographical memory. They have suggested the possibility that ALF and AA might have a more diffuse physiological basis rather than being a consequence of discrete structural damage [58].

Milton et al, 2010, studied AA in 14 TEA patients and compared with 12 healthy controls. They found that performance on standard tests of anterograde memory was normal. Severe autobiographical amnesia was noted extending across the entire lifespan. Personal semantic memory was found to be mildly impaired, more strikingly for midlife years. There were limited deficits of public semantic memory for recent decades [59].

Muhlert et al, 2012, was conducted with a more robust methodology to overcome the drawbacks of previous studies. In this study they have included patients with TLE and Idiopathic Generalised Epilepsy (IGE) along with matched healthy controls and assessed for ALF. ALF was noted in TLE group between 30-min and three-weeks, but not between 40-s and 30-min. Rates of forgetting were not significantly different between patients with IGE and controls. No association was found between ALF and seizures during the three-week delay or number of antiepileptic drugs [10].

Proposed mechanisms:

In a classic study of patients who underwent temporal lobectomy for intractable epilepsy due to hippocampal sclerosis, it was shown that delayed recall was impaired with

hippocampal sclerosis and delayed recall for verbal tasks were affected for left hippocampal sclerosis [60].

A more recent study had shown that working memory was impaired in persons with left or right hippocampal sclerosis. In addition, there was impaired integrity of both gray and white matter [61]. These studies have shown the important role of hippocampus in encoding memory. As a results damage to the hippocampus as with hippocampal sclerosis in temporal lobe epilepsy there can be difficulties with working memory and delayed recall. In contrast to the role of hippocampus and other mesial temporal structures, the temporal neocortex is involved with long term memory. Studies have shown that the lateral temporal lobe which consists mostly of neocortex plays a crucial role in storage of knowledge and personal experiences [62,63].

Two sub-domains of memory that affected by TLE are the working memory (WM) and episodic memory related deficits. Among all the sub-domains of memory, WM or Short-term memory (STM) is a transient trace of information temporarily stored that requires consolidation by the support of the medial temporal lobe (MTL) to be converted into a more stable status of long-term memory (LTM). WM impairment carries immense clinical importance not only because of the disability that it leads to, but also because of its association with long-term memory (LTM). This association has been highlighted in the recent models of WM in the role of the "episodic buffer" that link it to LTM systems [3]. LTM will also be affected if STM is impaired in TLE.

Theories of consolidation:

According to traditional models, information has been encoded into long-term memory through the process of 'consolidation', which renders the memory trace progressively less vulnerable to disruption [64]. The 'Standard theory of Consolidation' (STC) of Squire and

Alvarez hypothesised that this process, involves a gradual reorganization of the memory trace and can be divided into two LTM consolidation processes – the fast and the slow processes [65]. They have proposed that the fast consolidation process is mediated by the MTL structures and the slower neocortical consolidation by the repeated and synchronous firing of hippocampal-neocortical connections process. This process may continue for weeks, months or even years but it is often assumed that its function can be assessed at relatively brief delays with standard neuropsychological tests. The most straight forward hypothesis for ALF would be the disruption of this extended periods of consolidation of memory, either by epileptiform activity or by the structural abnormality itself which is also causing the epilepsy.

The 'Multiple Trace theory' (MTT) (Nadel et al, 1997), suggests that certain types of declarative memories, true 'episodic' memories, remain dependent on the hippocampus regardless of their age, and that their rehearsal and reactivation lead to the creation of multiple memory traces within the MTL [66]. The MTT allows for the possibility that pathology restricted to the MTL may impair both anterograde and remote episodic memory. Whether it would predict the particular combination of features observed in TEA—subtle hippocampal pathology, normal or near normal anterograde memory on standard tests, marked ALF and AA, is less clear. Computational modelling of medial temporal lobe function, and its pathologies, may help to clarify whether this cluster of phenomena is compatible with the predictions of MTT.

The STC, on the other hand, can readily explain the occurrence of ALF in the context of hippocampal pathology. But it cannot so readily explain the occurrence of AA, assuming that this is not the result of impaired initial acquisition. To explain this, the STC must invoke some other factor, perhaps disruption of distributed neocortical memory traces by epileptiform activity.

Etiology and pathophysiology of ALF:

Several contributory mechanisms have been hypothesised:

1. Clinical or subclinical seizure activity.
2. Structural or other underlying brain pathology.
3. An adverse effect of anticonvulsant medication.
4. Psychological mechanisms.

O'Connor et al, 1997, has documented improvement in memory performance in a single case of TLE after control of seizures [44]. Mameniskiene et al, 2006, found a positive correlation between long-term forgetting and both (i) manifest seizures during the experimental period and (ii) subclinical epileptiform EEG activity [51]. As in the study by Blake et al, 2000, however, LTM was not found to correlate with the average seizure frequency reported by patients [46].

Many case studies discussed earlier had radiological evidence of structural brain pathology. Therefore, ALF might be a mild form of the amnesic syndrome, caused by subtle damage to the medial temporal lobes. In such case, the early acquisition should also be affected in patients with MTL structural abnormalities. The observation that some patients perform normally on standard tests yet exhibit ALF appears to argue against the existence of any defect in acquisition and initial retention of declarative memories [67].

Jokeit et al, 2005, has showed that amongst 162 patients with medically refractory epilepsy, higher serum levels of AED were associated with greater forgetting of both verbal and visual material over a 30-min delay [68]. It remains possible that the ALF can be due to anticonvulsants, but, it seems unlikely for a number of reasons: (i) patients with TEA complain of ALF prior to initiation of therapy; (ii) patients with TEA usually report that their memory improves once treatment is started [8,9]; (iii) the forgetting observed by Blake et al, (2000) was specific to the group of patients with left temporal lobe epilepsy [46]; (iv) the doses of

anticonvulsants used TEA patients, those who complain most profoundly of ALF, are generally low.

Studies assessed mood using the Hospital Anxiety and Depression Scale and found no correlation with very long-term memory performance [9,46,51]. Lewis and Kopelman, 1998, did not find accelerated forgetting in a group of depressed patients after equating initial levels of learning [69].

Etiology and pathophysiology of AA:

Six studies examined the possible causes of remote memory impairment in epilepsy with different methods and variables [39,53,55,70,71,72]. No study identified correlations between seizure related variables and autobiographical memory performance. Ricci et al, 2015, studied 21 patients TLE and regression analyses showed that the presence of a hippocampal lesion was particularly disruptive to consolidation over the first 24 hours, and that seizures were associated with memory decline over longer delays [73].

Some studies proposed that temporal lobe pathology, rather than the resulting seizures, was responsible for patients' difficulty in remembering the past [55,70,71]. Noulhiane et al, 2007, found correlations between autobiographical memory scores and the volumes of residual medial temporal lobe structures, particularly in the right hemisphere, as measured on MRI scans [53]. In other studies, remote semantic memory impairment was found to vary with aetiology [39,55], pre- or post-operative status [39] and the extent of operative excision [71]. Some studies have shown that, extensive retrograde amnesia occurs with minimal or no clinically apparent structural brain damage [9,11]. Kapur et al, 2000, has suggested that, in such cases, intermittent clinical or sub-clinical seizure activity beginning in the medial temporal lobes may disrupt neocortical networks that act as storage or retrieval sites for remote memory [45].

Lah et al, 2004 and 2006, have found a positive correlation between remote semantic memory loss and the number of anticonvulsants taken [71,72]. Interpretation of this result is confounded by the close relation between medication dose and the severity of epilepsy. However, TEA patients complain of profound autobiographical memory loss prior to starting treatment and are usually maintained on low dose monotherapy [9].

Mood disturbance is associated with memory dysfunction for public and autobiographical events [74]. It is important to consider the possibility that mood disturbance associated with epilepsy may be playing a role in AA. Butler et al, 2007, found no evidence of a difference in past or present diagnoses of major depression or generalized anxiety, and no correlation between scores on the Hospital Anxiety and Depression Scale and AA or ALF in patients with TEA [9].

Imaging correlates:

Addis et al, 2007, examined the impact of hippocampal damage on autobiographical memory network using functional MRI technique, in 11 patients with left TLE [41]. ABM-related activity was significantly reduced in patients compared to controls, in residual hippocampal tissue and across the AM network (including the medial prefrontal cortex, temporal poles, retrosplenial and lateral parietal cortex). The strength of connections involving the left hippocampus was also reduced in patients. These findings suggest that the left hippocampus has a crucial role the ABM network and its damage has significant consequences for the functional organization and connectivity of the neural network supporting ABM retrieval.

Butler et al, 2009, analysed MRI data from 41 patients with TEA and 20 matched healthy controls, using manual volumetry and voxel-based morphometry (VBM). They studied the correlation between regional brain volumes, clinical and neuropsychological data. Manual

volumetry identified subtle hippocampal volume loss in the TEA group. Both manual volumetry and VBM revealed correlations between medial temporal lobe atrophy and standard anterograde memory scores, but no relation between atrophy and ALF or remote autobiographical memory. They have suggested the possibility that ALF and AA might have a more diffuse physiological basis rather than being a consequence of discrete structural damage [58].

Butler et al, 2012, studied patients with TEA and found no significant correlations between volumetric measures of the hippocampus and indices of ALF or AA [75]. Post-mortem investigations in a patient with TLE who showed ALF and AA, yielded evidence of neuronal loss and gliosis in regions of both the right and the left hippocampus. Neuronal loss and gliosis were more evident in anterior than posterior hippocampus. This shows that the unusual forms of long-term forgetting seen in some patients with TLE have no gross anatomical correlate. Hence, subtle structural damage or subtle functional disturbance, perhaps in the form of subclinical epileptiform activity, underly epilepsy-related long-term amnesia.

Ricci et al, 2015, studied 21 patients TLE, with and without hippocampal lesions. Regression analyses showed that a hippocampal lesion was particularly disruptive to consolidation over the first 24 hours, and that seizures were associated with memory decline over longer delays [73]. They hypothesized that consolidation of autobiographical experiences involves multiple mechanisms and they operate over different time frames.

Atherton et al, 2018, studied 15 TEA patients with ALF and healthy matched controls [76]. They studied encoding related brain activity in these patients using memory paradigms in fMRI. They found reduced activity of the left hippocampus for the items, patients would go on to forget, together with differential activity levels in other parts of the wider memory network. This abnormal encoding activity may reflect the formation of substandard memory representations that are vulnerable to interference. A similar type of a study of 23 patients with

TLE found that ALF at 72 hours was associated with reduced functional connectivity between the affected anterior hippocampus and unaffected lateral temporal cortex [77].

Memory dysfunction in Idiopathic Generalised Epilepsy (IGE):

Some studies have examined ALF in IGE patients. Muhlert et al, 2012, studied adults and was conducted with a more robust methodology compared to previous studies of TLE patients to overcome their drawbacks [10]. In this study they have included patients with TLE and Idiopathic Generalised Epilepsy (IGE) along with matched healthy controls and assessed for ALF. ALF was noted in TLE group between 30-min and three-weeks, but not between 40-s and 30-min. Rates of forgetting were not significantly different between patients with IGE and controls. No association was found between ALF and seizures during the three-week delay or number of antiepileptic drugs. Beilharz et al, 2020, also did not find evidence for ALF in adults with IGE [78].

Davidson et al, 2007, was conducted in children with IGE and found evidence of ALF but attributed this finding to poor initial learning efficiency [79]. Gascoigne et al, 2012, studied ALF in 20 children with IGE (41 controls) and whether it relates to epilepsy severity [80]. They found significant ALF in patients for verbal memory and greater epilepsy severity was associated with poorer memory and proposed that seizures themselves may disrupt long-term memory consolidation. Grayson-Collins et al, 2017, has assessed 18 children with IGE with verbal memory testing and at two years follow up, ALF was apparent, although epilepsy severity reduced, and seizures resolved in many children [81]. This result, in contrast to the dominant conceptualisation of ALF being a seizure related phenomenon, suggests that ALF may not be seizure related.

National Status:

A pubMed search for epilepsy and memory in the title published from India yielded only a few reports and studies. There had been little systematic research into the memory dysfunction in epilepsy from our country. Recent study had reported a case of childhood onset epilepsy with episodic fugue like state as the sole ictal manifestation [82]. A study was conducted which pointed out the imbalance in the monoamine levels, elevated nitrosative and acetylcholine esterase activity in the cortex and hippocampus of people with epilepsy [83]. Recent study showed that impairment of memory; language and executive function are common among patients with drug refractory epilepsy. The most prevalent impairment is in executive function. There is no significant difference in the degree, prevalence, or selectivity of impairment in either of the three domains, between the TLE versus ETLE groups [84]. Shah et al, 2016, has studied memory performance of 106 patients who underwent anterior temporal lobectomy for TLE and found that group mean score analysis revealed no significant shifts in verbal or visual memory scores after left ATL, but significant improvements in verbal memory after right ATL [85]. There is paucity of data on long-term memory dysfunction in epilepsy, in our country. Our study would provide the baseline data on the performance of TLE patients in these special test batteries and comparison with healthy controls.

AIMS, HYPOTHESIS AND OBJECTIVES

AIMS OF THE STUDY

1. To characterize the pattern of memory dysfunction in patients with TLE.
2. To compare their performance in memory tests with healthy controls.

HYPOTHESIS

Temporal lobe epilepsy (TLE) predisposes to impaired long-term memory leading to accelerated long term forgetting (ALF) and autobiographical amnesia (AA). Assessment and diagnosis of this dysfunction requires special test batteries.

OBJECTIVES

1. To unravel special entities of LTM dysfunction in patients with TLE, by administering special test batteries and comparing with healthy controls.
2. To study associations between memory dysfunction and other baseline characteristics in patients with TLE.

MATERIALS AND METHODS

MATERIALS AND METHODS:

Study design and population:

This is a prospective cohort study. This study was carried out in the R. Madhavan Nayar Centre for Comprehensive Epilepsy care in the Sree Chitra Tirunal Institute for Medical Sciences. This study was restricted to adult patients with Temporal Lobe Epilepsy that were scheduled for long term video EEG monitoring in the epilepsy program in SCTIMST. These cases were already well worked up for the epilepsy from clinical and imaging viewpoints.

Sample size: No such study had been carried out on this topic from India. Looking at the published literature from abroad, a sample size of 40 would suffice. Sample size was estimated based on the effect size noted in a previous, similar studies, where ALF was noted in around 20-25% of healthy individuals and 45-50% TLE patients. Also, 62% of TLE patients performed at least 2 SDs below healthy controls on AMI. Keeping in mind this incidence, to achieve 80% power of the study with an alpha error of 5%, the minimum sample size estimated in each group was 50.

Sample size formula:

To compare two proportions, each group need to have a minimum sample size of

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 (P_1 Q_1 + P_2 Q_2)}{(P_1 - P_2)^2}$$

Where $Z_{1-\alpha/2}$ is the 97.5th percentile of a standard normal distribution for α=0.05 that is equal to 1.96, $Z_{1-\beta}$ is the 80th percentile of a standard normal distribution for β=.20 that is equal to 0.84, P_1 and P_2 are the expected proportions in the 2 groups compared, Q_1=1-P_1 and Q_2=1-P_2.

Sampling method: Consecutive patients on follow up in the Epilepsy Clinic, who satisfy the eligibility criteria, will be included.

Controls: We recruited age and education matched controls for this study from volunteers, casual visitors to the hospital and relatives of the patients who are willing to participate in this study.

Education details will be obtained, and the participants will be classified into elementary (completed V standard), secondary (completed X standard), higher secondary (completed plus 2), graduate and postgraduate levels for matching.

Inclusion criteria:

Any patient with active epilepsy (one or more seizures in the past five years or seizure free on antiepileptic drugs); age between 18 - 47 years and scheduled for a prolonged VEEG monitoring (for one to five days) will be screened

- The patient should have temporal lobe epilepsy as suggested by typical seizure semiology consistent with complex partial seizure of temporal lobe origin plus any one of the following (a) Interictal epileptiform discharges in the EEG confined to the anterior or mid temporal electrodes (b) MRI evidence of lesion in the temporal lobe – medial temporal sclerosis, tumours or gliosis.

Exclusion criteria:

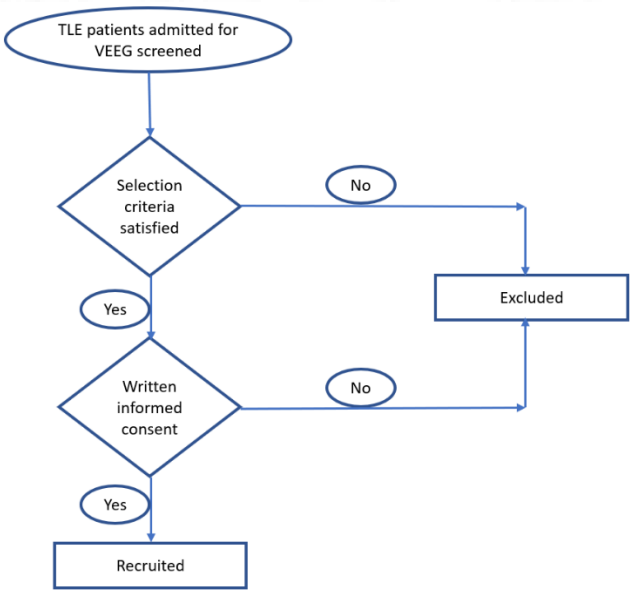
Any patient with any one of the following will be excluded:

1. Progressive neurological disorders.
2. Lesions in the MRI in any location other than temporal lobe.
3. IQ less than 80.
4. Significant mental depression.
5. Pregnant women.
6. Medical conditions that may interfere with the test procedures or may influence the outcome measures.

Methodology:

The potential candidates for the study were identified from the epilepsy service and were briefed about the study and the procedures involved. An informed signed and witnessed consent was taken from every participant. The screening process for recruitment is given in Figure 1.

Figure 4: Screening process for recruitment of the cases



The clinical details of the patients related to epilepsy, use of antiepileptic drugs, other co morbidities and general lifestyle of the patient was extracted from the medical records and from personal interviews. The EEG and imaging details of the patients were recorded.

Neuropsychological assessment:

Standard tests for IQ, and memory were administered at the time of recruitment, which included, Weschler Adult Performance Intelligence Scale (WAPIS), Verbal Adult Intelligence Scale (VAIS) (Appendix) [86].

Rey Auditory Verbal Learning Test (RAVLT), Rey complex figure test (Appendix) were administered at baseline, 30 minutes, and 5 days, for assessment of accelerated long-term forgetting [87,88]. Maximum score for RAVLT was 15 and for RCFT was 32.

Pearson Autobiographical memory interview (AMI) was administered for assessment of autobiographical memory (Kopelman et al, 1989) [33]. It has 'personal semantic' and 'autobiographical incidents' domains and each of these domains are assessed in the:

1. Childhood - (score of 21 for personal semantic and 9 for autobiographical incidents)
2. Early adult life - (score of 21 for personal semantic and 9 for autobiographical incidents)
3. Recent life - (score of 21 for personal semantic and 9 for autobiographical incidents)

The maximum total score of AMI is 90 (63 for personal semantic domain and 27 for autobiographical incidents domain).

The same set of neuropsychological tests were administered to TLE patients and controls. The administration of these neuropsychological tests was done by a qualified neuropsychologist. AMI was translated to participant's mother tongue by the neuropsychologist and administered.

Statistical analyses:

Analyses of all data sets were performed by using the Medical Statistics Software SPSS, Version 25.0 (IBM, Armonk, New York) with the help of a medical statistics expert. The comparison of baseline characteristics and different neuropsychological test variables between TLE and control groups will be done using independent student t-tests or Mann Whitney U tests, as appropriate. Gender distribution of cases and controls was compared using Fisher's exact test. To compare long-term forgetting rates of the patient and control groups, we conducted repeated-measures analyses of variance (ANOVA), with factors of participant group and delay (immediate, 30 minutes and 5 days), using recall score as the dependent variable.

The Greenhouse–Geisser correction for nonsphericity was applied where necessary. A p-value <0.05 was chosen to control for multiple comparisons.

Ethical considerations:

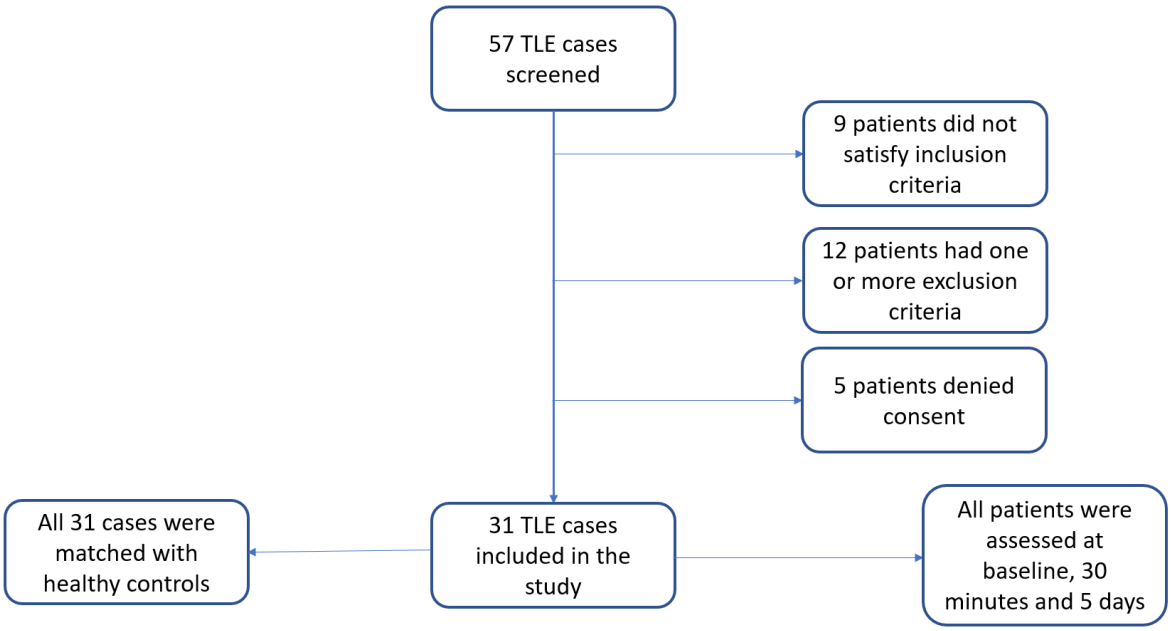
This study has the approval of the Institutional Ethics Committee (IEC Regn No. ECR/189/Inst/KL/2013/RR-16) and informed consent was obtained from all the cases and controls.

RESULTS

RESULTS

This hospital based prospective cohort study included TLE patients admitted in comprehensive epilepsy care unit, SCTIMST for long-term VEEG monitoring during a two-year time (2019-2020). Of the patients admitted for long-term VEEG monitoring 2019 to 2020, 57 TLE patients were identified of which 31 patients were fulfilling the inclusion criteria and were included in the study (Figure 2). All 31 patients were assessed at baseline, 30 minutes, and 5 days. No loss to follow-up was present. Twenty-six patients were not included in the study, as they had one or more exclusion criteria, did not satisfy inclusion criteria, or denied consent. All 31 TLE cases were matched with healthy controls. Age and education variables were considered for matching.

Figure 5: CONSORT diagram of the study

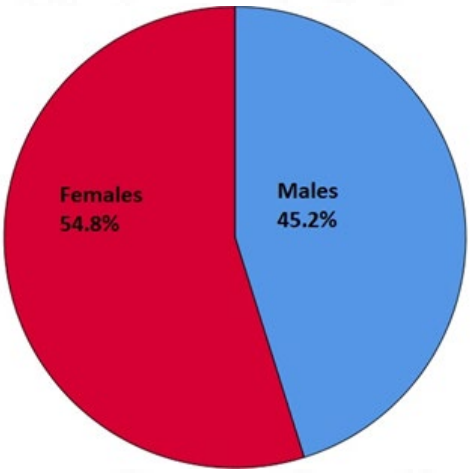


CHARACTERISTICS OF THE TLE group:

Gender distribution of TLE patients:

In our study (Figure 3), out of 31 cases males were 14 (45.2%) and females were 17 (58.8%).

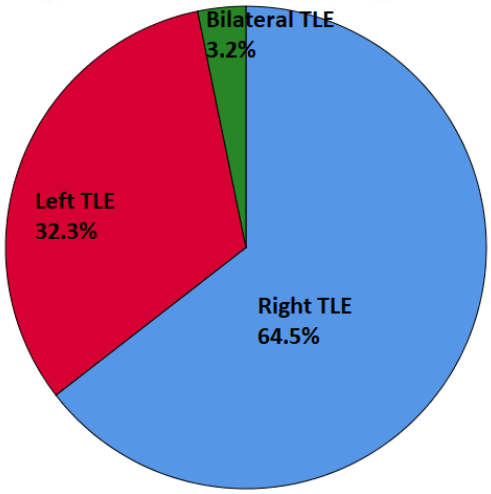
Figure 6: Gender distribution of cases (n=31)



Laterality of TLE:

The diagnosis and lateralisation into right, left or bilateral TLE was made based on the imaging, video EEG, ictal semiology, ictal and interictal electrophysiology data. Out of the 31 TLE cases, 20 (64.5%) were right TLE, 10 (32.3%) were left TLE and 1 (3.2%) was bilateral TLE (Figure 4).

Figure 7: Laterality of TLE in the patient cohort (n=31)



Other baseline characteristics of the TLE group:

Table 1: Baseline characteristics of the TLE group

Variable	Mean (n=31)	Standard deviation
Age of the patient (in years)	29.03	8.38
Years of education (in years)	17.42	3.07
Age of seizure onset (in years)	17.32	10.71
Duration of epilepsy (in years)	12.10	7.68
Recent seizure frequency* (per month)	2.5	3.25
Number of AEDs	2.13	0.81
PIQ	96.90	13.65
VIQ	100.23	19.80
FSIQ	98.81	14.41

*Seizure frequency documented in the preceding 1 year expressed in Median and interquartile range (IQR)

PIQ: Performance IQ, VIQ: Verbal IQ, FSIQ: Full scale IQ (Appendix), AED: Antiepileptic drug

Age of seizure onset in the TLE group was 17.32 (+/- 10.71) years and the duration of seizures at the time of enrolment into the study was 12.1 (+/- 7.68) years. Seizure frequency in the 1-year preceding enrolment was 2.5/month (IQR=3.25). These patients were on 2.13 AEDs on an average. As mentioned in the criteria for participation in the study, PIQ, VIQ and FSIQ were more than 80.

Neuropsychology data of the TLE group:

Verbal memory:

Table 2: Verbal memory – RAVLT data of the TLE group

Variable	Mean (n=31)	Standard deviation
T1-RAVLT (15)	6.19	1.85
T2-RAVLT (15)	9.03	1.82
T3-RAVLT (15)	10.61	2.60
T4-RAVLT (15)	12.16	2.08
T5-RAVLT (15)	12.45	1.73
30M-RECALL-RAVLT (15)	10.58	2.28
30M-RECOG-RAVLT (15)	14.00	1.44
30M-CE-RAVLT	0.81	1.92
30M-OE-RAVLT	0.90	1.45
5D-RECALL-RAVLT (15)	7.48	2.19
5D-RECOG-RAVLT (15)	11.94	2.38
5D-CE-RAVLT	3.52	3.67
5D-OE-RAVLT	3.23	2.70

RAVLT: Rey Auditory Verbal Learning Test, T1 to T5: Trial1 to 5 of RAVLT, 30M: 30 minutes, 5D: 5 days, RECALL: Recall, RECOG: Recognition, CE: Commission error, OE: Omission error

Participants were given a list of 15 unrelated words, repeated over five different trials, and were asked to repeat (Appendix) (T1 to T5 scores mentioned in Table 2). Another list of 15 unrelated words were given and the participant must again repeat the original list of 15 words and then again after 30 minutes (30M mentioned in Table 2, including recall, recognition, commission error and omission error). The same procedure was conducted at 5 days interval as part of long-term memory assessment. Similar testing was also done in the matched controls.

Visual memory:

Table 3: Visual memory – RCFT data of the TLE group

Variable	Mean (n=31)	Standard deviation
COPY-RCFT (32)	30.10	2.57
I-RECALL-RCFT (32)	19.16	5.12
30M-RCFT (32)	18.68	4.74
5D-RCFT (32)	16.85	4.51

RCFT: Rey-Osterrieth Complex Figure Test, COPY: Copying score of RCFT, IRECALL: Immediate recall, 30MRCFT: 30 minutes recall, 5DRCFT: 5 days recall

The RCFT employs a complex geometrical figure as the stimulus (Appendix); it comprises a large rectangle with horizontal and vertical bisectors, two diagonals, and additional geometric details. The test proceeds with the participant being asked to draw a copy of the presented figure as accurately as possible (COPY-RCFT), maximum score of 32. This task is followed by a distraction and a request to redraw the same figure from memory. In current study, participants were asked to redraw the figure immediately after copying (I-RECALL-RCFT), at 30 minutes (30M-RCFT) and 5 days (5D-RCFT) intervals. The same procedure has been applied to controls as well. Table 3 summarizes the various variables of the RCFT testing in the TLE cohort.

Autobiographical memory:

Autobiographical Memory Interview (AMI) was conducted for assessing the autobiographical memory. Table 4, 5 and 6, contain the scores in personal semantic, autobiographical incidents and total scores of the participants, respectively.

Personal semantic domain:

Table 4: AMI scores in 'Personal semantic domain'

Variable	Mean (n=31)	Standard deviation
Childhood (21)	17.43	2.71
Early adult hood (21)	17.42	3.28
Recent life (21)	16.76	3.16

Autobiographical incidents domain:

Table 5: AMI scores in 'Autobiographical incidents domain'

Variable	Mean (n=31)	Standard deviation
Childhood (9)	4.34	2.20
Early adult hood (9)	4.56	2.69
Recent life (9)	4.77	1.91

Total score on AMI:

Table 6: Total scores on AMI

Variable	Mean (n=31)	Standard deviation
T-PS-AMI (63)	51.61	8.45
T-AI-AMI (27)	13.71	6.10
T-AMI (90)	65.32	13.25

T: Total, PS: Personal semantic, AI: Autobiographical incidents, AMI: Autobiographical Memory Interview

Tables 2 to 6 provide the baseline data of the TLE patients in the neuropsychological tests. The speciality in this assessment is the inclusion of assessment at 5 days interval (verbal and visual memory) and the assessment of autobiographical memory using AMI.

EEG and imaging details of TLE group:

EEG findings:

Table 7: Interictal discharges in EEG of the TLE group

Interictal discharges*	Right TLE (n=20)	Left TLE (n=10)	Bilateral TLE (n=1)
Ipsilateral IEDs	16	10	0
Bilateral IEDs	3	0	1
Contralateral IEDs	1	0	0

*predominant discharges, IED: Interictal epileptiform discharges

- In 20 patients diagnosed with right TLE, EEG findings showed right temporal IEDs in 16 patients, bilateral in 3 and predominantly left temporal IEDs in 1 patient.
- In 10 patients diagnosed with left TLE, EEG findings showed left temporal IEDs in all 10 patients.

- In 1 patient diagnosed with bilateral temporal epileptogenicity, EEG findings showed interictal epileptiform discharges from bilateral temporal regions in 50:50 ratio.

Imaging findings:

Table 8: Findings in MRI brain of the TLE group

MRI findings	Right TLE (n=20)	Left TLE (n=10)	Bilateral TLE (n=1)
Ipsilateral MTS	10	4	0
Vascular lesion/Developmental neoplasm	3	0	0
FCD	3	0	0
B/L medial temporal HI	0	2	1
Contralateral MTS	0	1	0
Normal	4	2	0
Not available	0	1	0

MTS: Mesial temporal sclerosis, FCD: Focal cortical dysplasia, HI: T2/FLAIR hyperintensity

- In 20 patients diagnosed with right TLE, MRI findings showed right MTS in 10 patients, right temporal vascular lesion/developmental neoplasm in 3 (cavernoma, ganglioglioma, dysembryoblastic neuroepithelial tumour in each of them), FCD in 3 and structural normality in 4 patients.
- In 10 patients diagnosed with left TLE, MRI findings showed left MTS in 4 patients, right MTS in 1, bilateral medial temporal T2/FLAIR hyperintensities in 2 and structural normality in 2 patients (Imaging was not available in 1 patient).
- In 1 patient diagnosed with bilateral temporal epileptogenicity, imaging showed bilateral medial temporal T2/FLAIR hyperintensities.

CASES VERSUS CONTROLS:

Baseline characteristics:

Table 9: Comparison of the baseline characteristics of cases and controls

Variable	Mean (S.D.) of cases (n=31)	Mean (S.D.) of controls (n=31)	p-value
Age (in years)	29.03 (8.38)	31.19 (7.88)	0.300
Sex (Males/Females)	14/17	13/18	0.798
Years of education	17.42 (3.07)	16.94 (2.71)	0.513
PIQ	96.90 (13.65)	101.45 (11.16)	0.156
VIQ	100.23 (19.8)	104.19 (14.86)	0.376
FSIQ	98.81 (14.41)	102.87 (11.59)	0.226

PIQ: Performance IQ, VIQ: Verbal IQ, FSIQ: Full scale IQ

Age, sex distribution and years of education of the cases and controls were comparable. PIQ, VIQ and FSIQ of the cases and controls were also not significantly different with a p value of more than 0.05.

We have divided the educational status into 5 classes: Elementary school, Secondary school, Higher secondary, Graduate and Postgraduate.

Table 10: Distribution of participants into education classes

Education class	Cases (n=31)	Controls (n=31)
Elementary school	0	0
Secondary school	2	2
Higher secondary	8	8
Graduate	18	18
Postgraduate	3	3

Neuropsychological tests: Cases vs Controls:

Verbal memory:

Table 11: RAVLT scores – Cases vs Controls

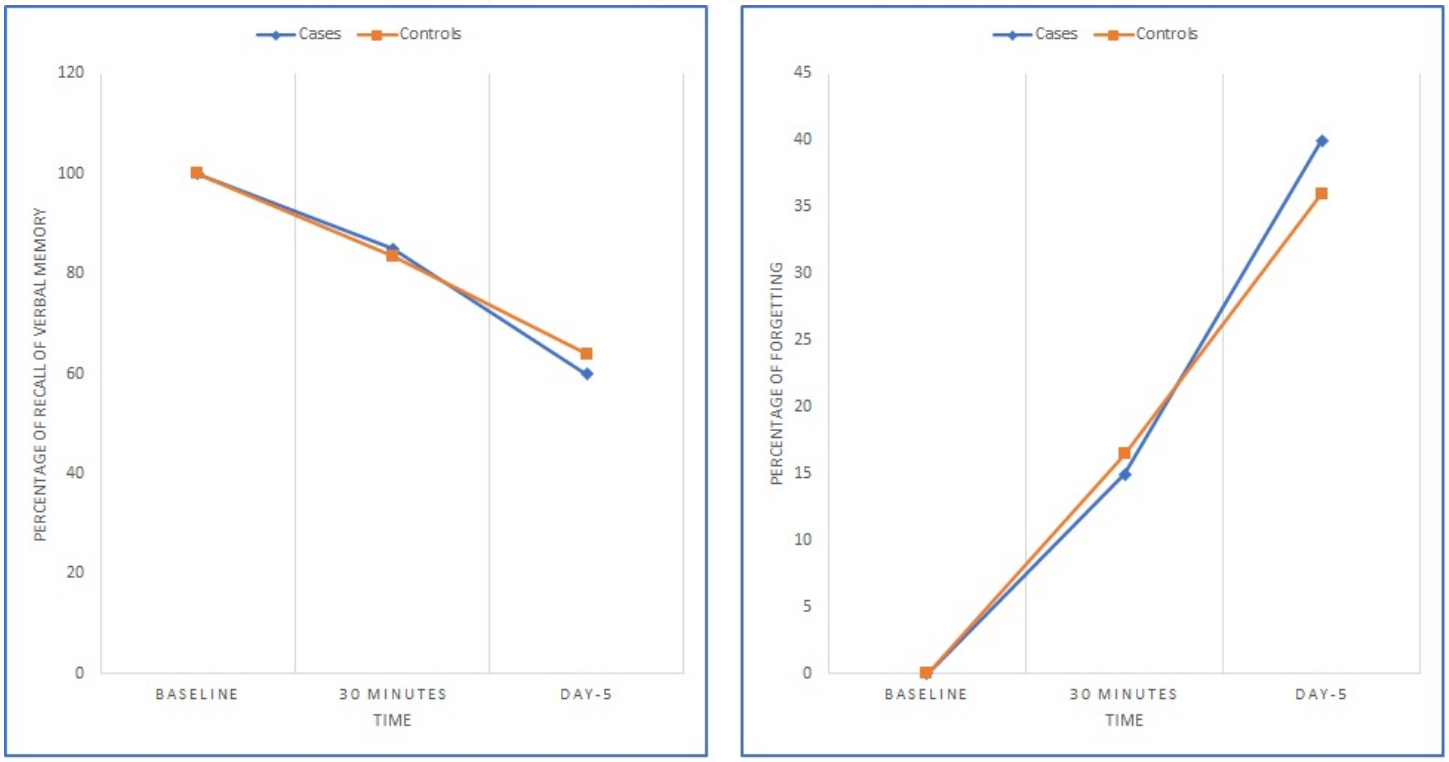
Variable	Mean (S.D.) of cases (n=31)	Mean (S.D.) of controls (n=31)	p-value
T1-RAVLT (15)	6.19 (1.85)	7.29 (2.49)	0.054
T2-RAVLT (15)	9.03 (1.82)	10.03 (2.2)	0.056
T3-RAVLT (15)	10.61 (2.60)	11.94 (2.55)	0.048
T4-RAVLT (15)	12.16 (2.08)	12.55 (2.25)	0.485
T5-RAVLT (15)	12.45 (1.73)	13.03 (2.02)	0.229
30M-RECALL-RAVLT (15)	10.58 (2.28)	10.87 (2.04)	0.599
30M-RECOG-RAVLT (15)	14.00 (1.44)	14.32 (0.87)	0.29
30M-CE-RAVLT	0.81 (1.92)	1.29 (2.56)	0.403
30M-OE-RAVLT	0.90 (1.45)	0.68 (0.87)	0.459
5D-RECALL-RAVLT (15)	7.48 (2.19)	8.35 (2.07)	0.113
5D-RECOG-RAVLT (15)	11.94 (2.38)	12.9 (1.87)	0.08
5D-CE-RAVLT	3.52 (3.67)	2.29 (2.56)	0.132
5D-OE-RAVLT	3.23 (2.70)	2.1 (1.87)	0.061

RAVLT: Rey Auditory Verbal Learning Test, T1 to T5: Trial1 to 5 of RAVLT, 30M: 30 minutes, 5D: 5 days, RECALL: Recall, RECOG: Recognition, CE: Commission error, OE: Omission error

- In 20 patients diagnosed with right TLE, MRI findings showed right MTS in 10 patients, right temporal vascular lesion/developmental neoplasm in 3 (cavernoma, ganglioglioma, dysembryoblastic neuroepithelial tumour in each of them), FCD in 3 and structural normality in 4 patients.

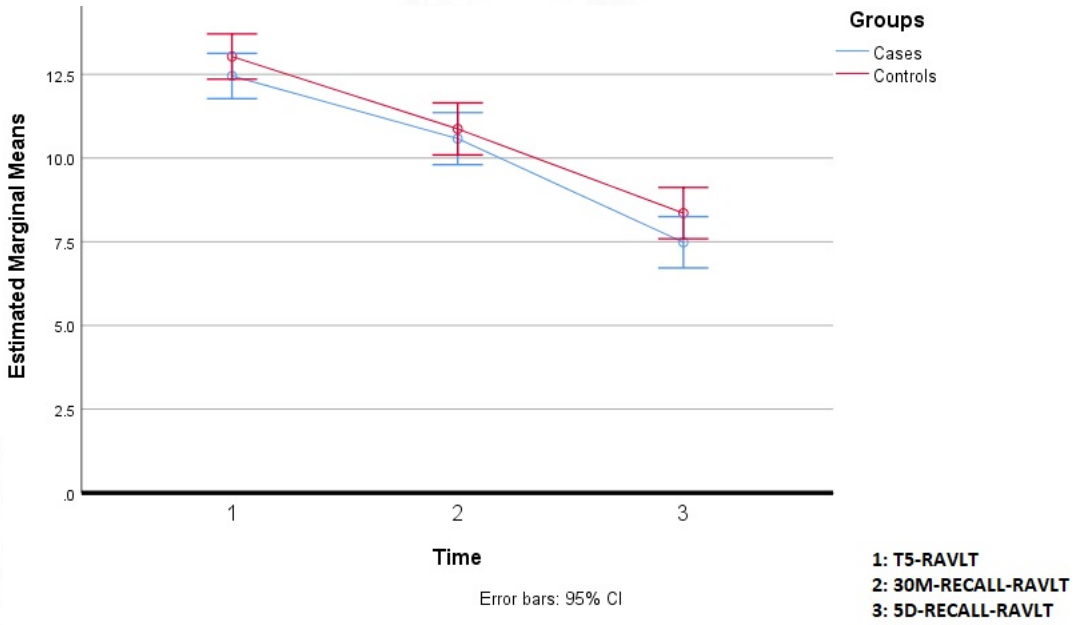
- In 10 patients diagnosed with left TLE, MRI findings showed left MTS in 4 patients, right MTS in 1, bilateral medial temporal T2/FLAIR hyperintensities in 2 and structural normality in 2 patients (Imaging was not available in 1 patient).
- In 1 patient diagnosed with bilateral temporal epileptogenicity, imaging showed bilateral medial temporal T2/FLAIR hyperintensities.

Figure 8: Accelerated long-term forgetting in TLE



ALF assessment (Verbal memory):

Figure 9: Trend of performance of cases vs controls in verbal memory (RAVLT) (during baseline, 30 minutes, and 5 days)



The RAVLT recall scores of cases were → baseline (M=12.45, SD=1.73), 30 minutes (M=10.58, SD=2.28), and 5 days (M=7.48, SD=2.19). The corresponding scores of controls were → baseline (M=13.03, SD=2.02), 30 minutes (M=10.87, SD=2.04), and 5 days (M=8.35, SD=2.07). A repeated measures ANOVA, between the groups (cases and controls) indicated no significant change in verbal memory over time, p = 0.514.

Visual memory:

Table 12: RCFT scores – Cases vs Controls

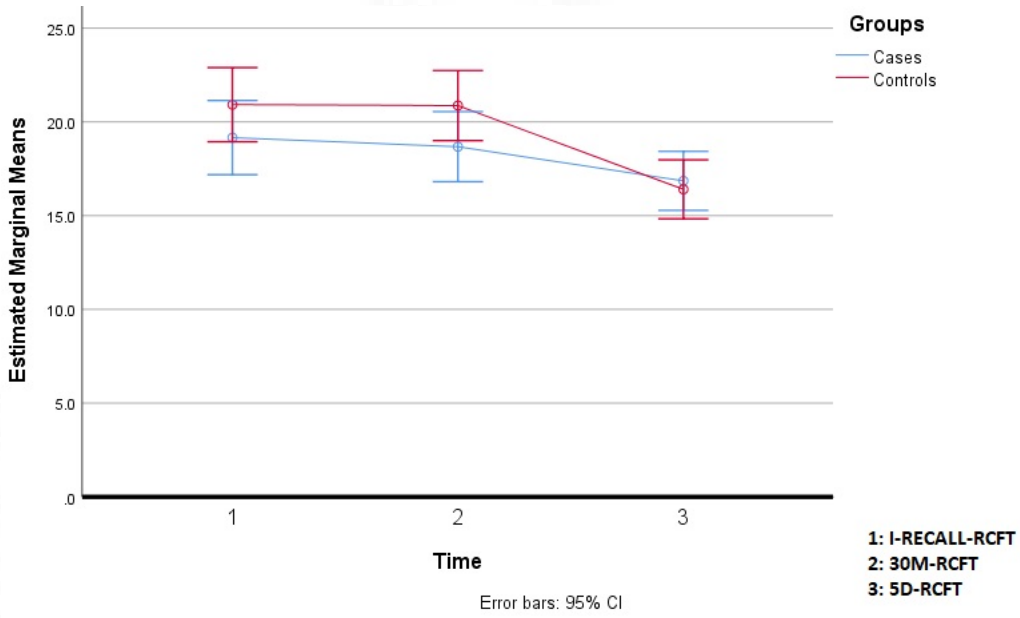
Variable	Mean (S.D.) of cases (n=31)	Mean (S.D.) of controls (n=31)	p-value
COPY-RCFT (32)	30.10 (2.57)	31.29 (1.27)	0.024
I-RECALL-RCFT (32)	19.16 (5.12)	20.92 (5.87)	0.214
30M-RCFT (32)	18.68 (4.74)	20.87 (5.63)	0.102
5D-RCFT (32)	16.85 (4.51)	16.40 (4.24)	0.686

RCFT: Rey-Osterrieth Complex Figure Test, COPY: Copying score of RCFT, IRECALL: Immediate recall, 30MRCFT: 30 minutes recall, 5DRCFT: 5 days recall

There was no significant difference between the baseline visual learning (I-RECALL-RCFT) (p=0.214). Follow-up assessment of visual memory (RCFT scores) at 30 minutes and 5 days, were not significantly different between cases and controls, p- values were >0.05 (0.102 and 0.686 respectively).

ALF assessment (Visual memory):

Figure 10: Trend of performance of cases vs controls in visual memory (RCFT) (during baseline, 30 minutes, and 5 days)



The RCFT scores of cases were → baseline (M=19.16, SD=5.12), 30 minutes (M=18.68, SD=4.74), and 5 days (M=16.85, SD=4.51). The corresponding scores of controls were → baseline (M=20.92, SD=5.87), 30 minutes (M=20.87, SD=5.63), and 5 days (M=16.40, SD=4.24). A repeated measures ANOVA, between the groups (cases and controls) indicated significant decline in RCFT scores in controls over time, p = 0.004.

Autobiographical memory:

Personal semantic memory:

Table 13: Personal semantic AMI scores – Cases vs Controls

Variable	Mean (S.D.) of cases (n=31)	Mean (S.D.) of controls (n=31)	p-value
Childhood (21)	17.43 (2.71)	18.13 (2.33)	0.284
Early adult life (21)	17.42 (3.28)	19.05 (2.37)	**0.029**
Recent life (21)	16.76 (3.16)	19.06 (1.43)	**<0.001**
T-PS-AMI (63)	51.61 (8.45)	56.24 (5.12)	**0.011**

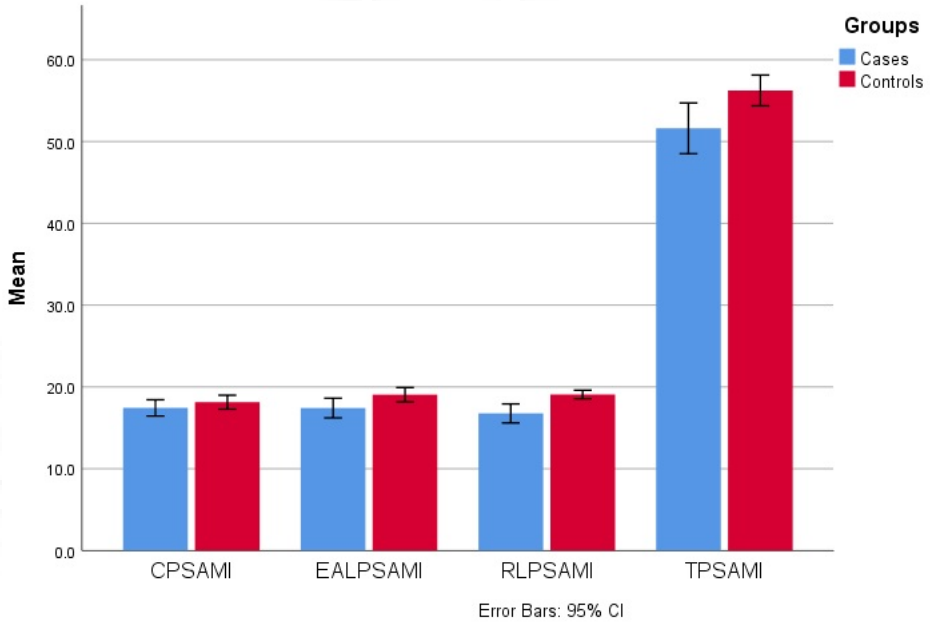
T: Total, PS: Personal semantic, AMI: Autobiographical Memory Interview

The personal sematic AMI scores of cases were, childhood (M=17.43, SD=2.71), early adult life (M=17.42, SD=3.28) and recent life (M=16.76, SD=3.16). The corresponding scores of controls were childhood (M=18.13, SD=2.33), early adult life (M=19.05, SD=2.37) and recent life (M=19.06, SD=1.43). There was a significant difference in the early adult life and recent life scores compared to controls (p-value of 0.029 & <0.001 respectively). There was no significant difference in childhood personal sematic scores (p=0.284). Bivariate analysis did not show any correlation between the age of seizure onset and childhood personal semantic AMI scores, in the TLE group.

Overall, personal semantic score of cases was (M=51.61, SD=8.45) and there was a significant difference compared to controls (M=56.24, SD=5.12), p=0.011. These results were reproduced with analysis using non-parametric tests as well.

AA assessment (Personal sematic memory):

Figure 11: Trend of performance of cases vs controls in personal semantic domain (AMI)



PS: Personal semantic, C: Childhood, EAL: Early adult life, RL: Recent life, T: Total, AMI: Autobiographical Memory Interview

Autobiographical memory:

Autobiographical incidents memory:

Table 14: Autobiographical incidents AMI scores – Cases vs Controls

Variable	Mean (S.D.) of cases (n=31)	Mean (S.D.) of controls (n=31)	p-value
Childhood (9)	4.34 (2.20)	5.03 (1.08)	0.121
Early adult life (9)	4.56 (2.69)	6.16 (1.1)	**0.003**
Recent life (9)	4.77 (1.91)	6.81 (1.25)	**<0.001**
T-AI-AMI (27)	13.71 (6.10)	18 (2.73)	**0.001**

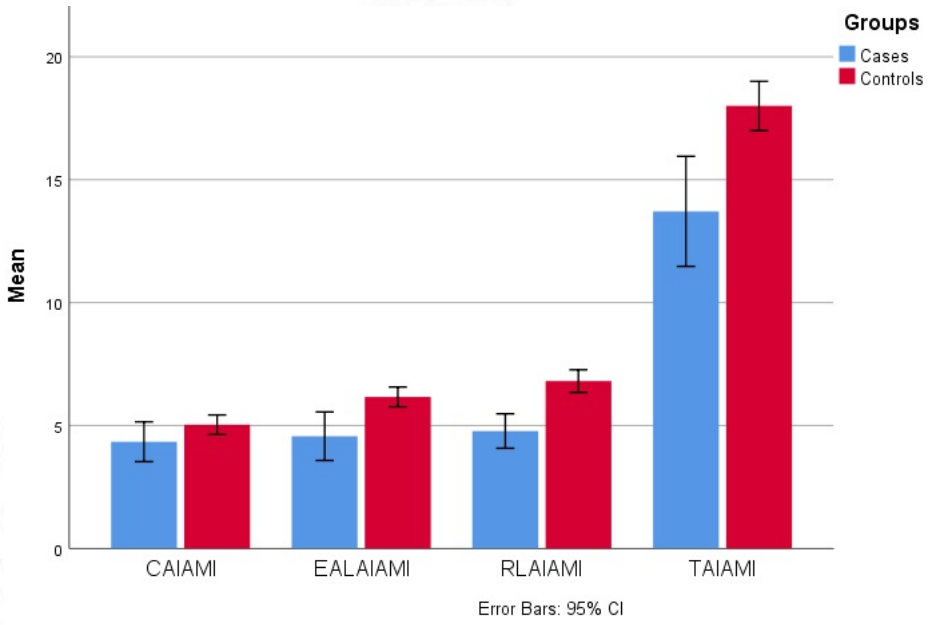
T: Total, PS: Personal semantic, AMI: Autobiographical Memory Interview

The autobiographical incidents AMI scores of cases were, childhood (M=4.34, SD=2.20), early adult life (M=4.56, SD=2.69) and recent life (M=4.77, SD=1.91). The corresponding scores of controls were, childhood (M=5.03, SD=1.08), early adult life (M=6.16, SD=1.1) and recent life (M=6.81, SD=1.25). There was a significant difference in the early adult life and recent life scores compared to controls (p-value of 0.003 & <0.001 respectively). There was no significant difference in childhood autobiographical incidents scores (p=0.121). Bivariate analysis did not show any correlation between the age of seizure onset and childhood autobiographical incidents AMI scores, in the TLE group.

Overall, autobiographical incidents score of cases was (M=13.71, SD=6.10) and there was a significant difference compared to controls (M=18, SD=2.73), p=0.001. These results were reproduced with analysis using non-parametric tests as well.

AA assessment (Autobiographical incidents memory):

Figure 12: Trend of performance of cases vs controls in autobiographical incidents domain (AMI)



AI: Autobiographical incidents, C: Childhood, EAL: Early adult life, RL: Recent life, T: Total, AMI: Autobiographical Memory Interview

The **total AMI scores (T-AMI)** of cases and controls were (M=65.32, SD=13.25) and (M=74.24, SD=6.88) respectively and there was a significant difference between the groups with a **p-value of 0.002**. These results were reproduced with analysis using non-parametric tests as well.

Bivariate analyses did not show correlation between autobiographical amnesia (T-AMI scores) and age of onset of epilepsy, duration of epilepsy, recent seizure frequency or number of antiepileptic drugs in the TLE group ($p>0.05$). Multivariate analysis could not be performed due to small sample size.

Sub-group analyses:

Right versus left TLE:

Table 15: Right TLE vs Left TLE (in the entire TLE cohort)

Variable	Mean (S.D.) in patients with right TLE (n=20)	Mean (S.D.) in patients with left TLE (n=10)	p-value
PIQ	99.75 (13.46)	88.9 (9.48)	0.031
VIQ	107.4 (18.63)	86.4 (15.62)	0.005
FSIQ	103.8 (14.12)	87.9 (8.62)	0.003

PIQ: Performance IQ, VIQ: Verbal IQ, FSIQ: Full scale IQ

The long-term verbal, visual and autobiographical memory scores of right TLE versus left TLE in the patients could not be assessed due to significant differences in the IQ scores of both the groups. P values of 0.031, 0.005 and 0.003 for PIQ, VIQ and FSIQ, respectively.

We have performed a sub-group analysis of 7 right TLE and 7 left TLE patients, matched for education, IQ, and age.

Table 16: Sub-group analysis of matched right TLE and left TLE cases

Variable	Mean (S.D.) in patients with right TLE (n=7)	Mean (S.D.) in patients with left TLE (n=7)	p-value
Age of the patient (in years)	29.71 (9.83)	28.71 (8.86)	0.845
Years of education (in years)	18.14 (3.72)	17.29 (2.36)	0.616
Duration of epilepsy (in years)	11.14 (5.55)	11.86 (8.03)	0.850
Recent seizure frequency* (per month)	3.5 (58.75)	2.5 (2)	0.186
Number of events during 5-day assessment period	2.71 (2.56)	2.14 (2.54)	0.683
Number of AEDs	1.86 (0.69)	257 (1.13)	0.180

PIQ	98.00 (14.46)	91.71 (8.94)	0.347
VIQ	99 (19.10)	90.29 (15.40)	0.366
FSIQ	98.86 (15.34)	91.29 (7.99)	0.269
T1-RAVLT (15)	4.86 (0.90)	5.57 (2.07)	0.419
T2-RAVLT (15)	8.57 (2.15)	8.86 (1.46)	0.776
T3-RAVLT (15)	10.43 (2.44)	9.57 (2.64)	0.540
T4-RAVLT (15)	12.43 (1.72)	11 (2.58)	0.246
T5-RAVLT (15)	12.71 (1.38)	11.29 (2.43)	0.201
30M-RECALL-RAVLT (15)	10.43 (2.37)	9.86 (2.19)	0.648
30M-RECOG-RAVLT (15)	13.29 (1.60)	13.57 (2.15)	0.783
30M-CE-RAVLT	0.29 (0.76)	1.29 (3.40)	0.462
30M-OE-RAVLT	1.71 (1.60)	1.43 (2.15)	0.783
5D-RECALL-RAVLT (15)	7.86 (3.13)	6.43 (1.13)	0.279
5D-RECOG-RAVLT (15)	12 (1.53)	12 (3.37)	1
5D-CE-RAVLT	3.71 (3.04)	5.43 (5.25)	0.469
5D-OE-RAVLT	2.29 (1.70)	3 (3.37)	0.626
COPY-RCFT (32)	31.29 (0.95)	29.57 (2.64)	0.132
I-RECALL-RCFT (32)	21.29 (5.61)	17.86 (4.34)	0.225
30M-RCFT (32)	20.14 (6.20)	17.71 (3.82)	0.395
5D-RCFT (32)	18.14 (6.04)	15.71 (2.75)	0.352
C-PS-AMI (21)	17.07 (3.02)	18.14 (1.07)	0.394
EAL-PS-AMI (21)	17.29 (3.93)	17.57 (1.27)	0.858
RL-PS-AMI (21)	15.28 (3.77)	17.64 (2.94)	0.217
T-PS-AMI (63)	49.64 (10.25)	53.36 (4.61)	0.399

C-AI-AMI (9)	3.43 (2.22)	4 (2.16)	0.635
EAL-AI-AMI (9)	3.79 (3.26)	4.57 (1.13)	0.559
RL-AI-AMI (9)	3.57 (2.30)	4.71 (0.95)	0.248
T-AI-AMI (27)	10.79 (7.32)	13.29 (2.62)	0.412
T-AMI (90)	60.43 (17.14)	66.64 (3.75)	0.367

*expressed as median and interquartile range (IQR)

PIQ: Performance IQ, VIQ: Verbal IQ, FSIQ: Full scale IQ

RAVLT: Rey Auditory Verbal Learning Test, T1 to T5: Trial1 to 5 of RAVLT, 30M: 30 minutes, 5D: 5 days, RECALL: Recall, RECOG: Recognition, CE: Commission error, OE: Omission error, RCFT: Rey-Osterrieth Complex Figure Test, COPY: Copying score of RCFT, IRECALL: Immediate recall, 30MRCFT: 30 minutes recall, 5DRCFT: 5 days recall

There was no significant difference found in the neuropsychological tests (verbal, visual and autobiographical) between the right TLE and left TLE patients. Repeated measures ANOVA did not show significant difference in RAVLT or RCFT scores over time, between right TLE and left TLE groups.

Seizures during study period:

Out of the 31 cases of TLE, 23 patients had seizure events during the study period and 8 were seizure free. Subgroup analysis of these cohorts did not show significant difference in the verbal, visual or autobiographical memory scores.

Structural abnormality on MRI:

Out of 31 cases of TLE, MR imaging was available for 30 cases, 24 showed structural abnormality and 6 were normal. Subgroup analysis of these cohorts did not show significant difference in the verbal, visual or autobiographical memory scores.

Left and right TLE separately with matched controls:

A sub-group analysis of left TLE and matched controls/right TLE and matched controls separately, also, showed similar results with significant differences in autobiographical memory **(p-values of 0.026 and 0.02 respectively for T-AMI scores)**, but not for ALF (verbal or visual).

DISCUSSION

DISCUSSION

Our study planned to assess novel entities of LTM dysfunction in TLE. We have included 31 patients with TLE and 31 healthy controls (age and education matched) in our study between 2019 and 2020. Special neuropsychological tests for long-term memory assessment were performed on all the cases and controls. Verbal memory was assessed using RAVLT and visual memory with RCFT, autobiographical memory was assessed using Autobiographical Memory Interview (AMI). Data of all the participants was included in the analyses and there was no attrition at follow up (30 minutes and 5th day assessment). Our study generated baseline data on LTM, in patients with TLE from India, using special test batteries. Significant differences between cases and controls were noted in autobiographical memory in the 'personal sematic' and 'autobiographical incidents' domains, in early adult life and recent life but not in childhood (Table 13 and Table 14). Assessment of verbal memory over a 5-day period showed a trend for accelerated long-term forgetting in cases compared to controls (Figure 5). Whereas, for visual memory there was a significant difference with a paradoxical fall of RCFT scores in controls at 5th day assessment (Figure 7).

The mean age of the 31 cases included in our study was 29.03 (±8.38) years, 14 (45.2%) were males and 17 (58.8%) were females (Figure 3). Out of the 31 TLE cases, 20 (64.5%) were right TLE, 10 (32.3%) were left TLE and 1 (3.2%) was bilateral TLE (Figure 4). Their mean FSIQ score was 98.81 (±14.41).

The trial 5 -RAVLT, 30 minutes recall and 5-day recall mean scores were 12.45 (±1.73), 10.58 (±2.28) and 7.48 (±2.19), respectively. The 30 minutes and 5-day recognition mean scores were 14 (±1.44) and 11.94 (±2.38), respectively. The 30 minutes and 5-day commission error mean scores were 0.81 (±1.92) and 3.52 (±3.67), respectively. The 30 minutes and 5-day omission error mean scores were 0.9 (±1.45) and 3.23 (±2.7), respectively. These values were similar to previous studies in TLE patients [9,53,89].

The immediate, 30 minutes and 5-day RCFT scores of cases were 19.16 (±5.12), 18.68 (±4.74) and 16.85 (±4.51), respectively. These scores were similar to previous studies in TLE patients [8,9,58,59,75]. The total AMI mean scores of 'personal semantic' and 'autobiographical incidents' domains of autobiographical memory were 51.61 (±8.45) and 13.71 (±6.1), respectively. These scores were similar to previous studies in TLE patients [8,90].

Accelerated long-term forgetting (ALF):

Verbal memory:

Our study showed a trend for accelerated long-term forgetting at 5th day assessment for verbal memory in patients with TLE compared to controls (Figure 5). These findings did not reach statistical significance probably due to small sample size. Cases and controls were comparable in age, sex distribution, education, and IQ. Some of the previous studies failed to show ALF in TLE [47,48,90], whereas majority of the studies have shown ALF for both verbal and visual memory in TLE [9,11,51,52]. In our study, cases and controls were comparable in age, sex distribution, education, and IQ.

Visual memory:

Assessment of visual memory scores at 5th day assessment showed a paradoxical drop in the RCFT scores of controls, reaching statistical significance. The RCFT scores of copying, immediate recall and 30-minute recall of cases and controls were comparable. This might be due to the fact that, the cases who were admitted for VEEG during the assessment period, had more chance for memorizing the figure during the 5-day interval compared to controls. The same factor would also be contributing to the non-significant difference of verbal memory scores at day 5. The other possible explanation would be the effect of outliers on the group data due to the small sample size.

Results were similar in sub-group analyses, which included, comparison of right and left TLE separately with their matched controls, presence or absence of medial temporal structural abnormality on MRI, presence or absence of seizures during the study period.

However, the effect of these factors cannot be completely excluded, and ALF might be due to the interplay of various coexisting factors along with TLE, such as AEDs, psychosocial factors, structural abnormality. So, the interpretation of these results should be done with caution. Further studies with a larger sample size and with a similar environment for both cases and controls during the study period are needed.

Autobiographical amnesia (AA):

Our results show significant differences in the autobiographical memory scores between cases and controls both in personal semantic and autobiographical incidents domains, in early adult life and recent life, but not in childhood. Correlation analysis did not find any effect of age of onset of seizures on the childhood AMI scores. Autobiographical amnesia was documented in TLE patients by multiple previous studies [8,9,11,46,53,58,59,75] and this particular pattern of AA, more for recent life and preserved early life (childhood in our study), was previously noted in some studies (Manes et al, 2005; Butler et al, 2007) [9,11]. This might indicate that LTM with time would become independent of the hippocampus which is in accordance with the Standard theory of consolidation [65]. Whereas some previous studies have shown AA across the entire life uniformly favoring the Multiple Trace theory of consolidation [53,66].

Bivariate analyses did not show correlation between autobiographical amnesia (T-AMI scores) and age of onset of epilepsy, duration of epilepsy, recent seizure frequency or number of antiepileptic drugs in the TLE group.

Analysis of left TLE and matched controls/right TLE and matched controls separately, also, showed similar results with significant differences in autobiographical memory (p-values of 0.026 and 0.02 respectively for T-AMI scores), suggesting that ABM might have bihemispheric representation. Sub-group analysis of matched left and right TLE patients did not show significant difference in AMI scores. Presence or absence of seizures during assessment period, presence or absence structural abnormality on imaging did not show significant difference in AMI scores. Sub-group analysis of patients with normal brain imaging compared to controls also showed significant differences in AMI scores. These analyses indicate that patients show autobiographical amnesia independent of the imaging abnormalities, laterality of the seizures and the occurrence of seizures during the 5-day interval. Studies on imaging correlation with AA done previously did not find any association with structural abnormalities in temporal lobes [56,73].

From our study, we can conclude that patients with TLE experience accelerated long-term forgetting and autobiographical amnesia. These deficits are not identified by the routine testing which assesses memory function at short intervals (30 minutes), as part of the neuropsychiatric test battery for PWE. Complaints of amnesia for recent life events with falsely normal routine memory assessment would invoke the possibility of psychogenic explanations. However, form our study and other similar studies, it is clear that these complaints might represent a true deficit that can be measured using appropriate neuropsychological tests.

Autobiographical memory is an important entity of human cognition. It helps in the remodeling of human behavior based on the previous life events and their consequences. Hence, their disruption along with a defect in anterograde learning in TLE would lead to severe disability [7]. There is a necessity for early recognition of autobiographical amnesia in these patients to plan early intervention.

Our study helps to provide baseline data on ALF and autobiographical amnesia in patients with TLE and would be considered as an early step towards standardizing memory testing protocol in PWE. We recommend inclusion of delayed memory assessment and assessment of autobiographical memory in the routine neuropsychiatric test battery of PWE (TLE in particular).

The presence of AA even in patients with normal imaging findings would indicate that ABM would occur with subtle structural changes or due to widespread network abnormalities. Functional brain imaging studies of activation patterns during autobiographical memory recall implicate the involvement of a wide network of brain regions, including frontal, temporal and posterior cortices, as well as cerebellum and sub-cortical structures [36,91]. The relative importance of these areas is likely to vary with factors such as the age of the memory, the emotional and perceptual content and the degree of personal significance [91].

Studies assessing encoding related brain activity in patients with TLE using memory paradigms in fMRI found reduced activity of the left hippocampus for the items, patients would go on to forget, together with differential activity levels in other parts of the wider memory network. This abnormal encoding activity may reflect the formation of substandard memory representations that are vulnerable to interference [76,77].

Future directions:

Future studies of patients with disproportionate impairments of autobiographical memory (as noted in our study), using both structural and functional imaging in life, together with post-mortem examination, will help to clarify which brain regions and processes contribute to this deficit. Studies to identify predictors of this memory dysfunction in patients with TLE are needed for early identification and intervention. Inclusion of EEG microstate analysis and advanced MRI sequences like DTI (Diffusion tensor imaging), VBM (Voxel based

morphometry) and functional MRI along with neuropsychological assessment would help identify predictors of memory dysfunction [92].

Ours is the first prospective study from India to assess the novel LTM deficits in patients with TLE. This study generated baseline data on the magnitude of accelerated long-term forgetting and autobiographical amnesia in people with TLE. It also unravels the need for inclusion of delayed memory assessment and autobiographical memory testing in the routine neuropsychiatric test battery of PWE. This study is important from the clinical perspective as the identification of these entities can help in early intervention and improving quality of life.

Strengths of the study

1. Prospective nature of the study and direct follow-up of all participants at 5th day of assessment.
2. Psychiatric or cognitive conditions that can affect the neuropsychiatric assessment have been excluded.
3. Validated Scores were used to separately assess the different realms of memory dysfunction in persons with epilepsy.
4. Sub-group analysis studying the effect of seizures during study period, structural brain abnormalities and laterality of TLE have been performed.

Limitations of the study

1. Multivariate analysis of possible confounders was not performed due to the small sample size.
2. Ceiling and floor effects of learning have not been taken into consideration.
3. Influence of socioeconomic status and language has not been analysed.

Table 17: Studies on ALF and AA in epilepsy

Study/Year	Sample size and participants	Short interval assessment	Special entities tested	ALF for verbal memory	ALF for visual memory	Autobiographical amnesia
Zeman et al.[8], 1998	10/TEA	Normal	AA	-	-	Present
Blake et al.[46], 2000	23/Epilepsy	Normal	ALF	Abnormal in left TLE	-	-
Manes et al.[11], 2005	7/TEA	Normal	ALF, AA	Present	Not significant	Present
Bell et al.[48], 2006	25/TLE	Abnormal for TLE group	ALF	Absent	-	-
Butler et al.[9], 2007	50/TEA	Normal	ALF, AA	Present	Present	Present
Milton et al.[59], 2010	14/TLE	Normal	AA	-	-	Present
Muhlert et al.[10], 2011	14/TLE	Normal	ALF	Present	Present	-
Butler et al.[75], 2012	22/TEA	Normal	ALF, AA	Present	Present	Present
Wilkinson et al.[52], 2012	27/TLE	Normal	ALF	Present	Present	-
Hoefeijzers et al.[93], 2013	24/TEA	Normal	ALF	Present	-	-
Cassel et al.[94], 2016	18/TLE	Normal	ALF	Present	-	-
Contador et al.[90], 2017	5/TLE	Normal	ALF	Absent	Absent	-
Miller et al.[89], 2017	44/Focal epilepsy	Normal	ALF	Present	Absent	-
Atherton et al.[76], 2018	15/TEA	Normal	ALF	Present	-	-
Beilharz et al.[78], 2020	14/IGE	Normal	ALF	Present	-	-
Our study	31/TLE	Normal	ALF, AA	Not significant	Absent	Present

CONCLUSIONS

CONCLUSIONS

- Our study provides data on novel entities of long-term memory dysfunction - accelerated long-term forgetting and autobiographical amnesia in TLE.
- TLE patients showed a trend for accelerated long-term forgetting at 5 days for verbal memory compared to controls.
- Autobiographical amnesia was significantly higher in TLE patients compared to controls in early adult life and recent life, both for personal sematic domain and autobiographical incidents independent of the laterality of TLE.
- The data from our study can help in standardising protocols to assess memory dysfunction in PWE and in further research.
- As accelerated long-term forgetting and autobiographical amnesia have disabling implications on quality of life, early identification is necessary for planning intervention strategies.

REFERENCES

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-82.
2. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia. 1999;40:631–6.
3. Leonardi M, Ustun TB. The global burden of epilepsy. *Epilepsia*. 2002;43 Suppl 6:21-25.
4. Corcoran R, Thompson P. Memory failure in epilepsy:retrospective reports and prospective recordings. Seizure1992;1:37-42.
5. Lømo T. The discovery of long-term potentiation. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 2003 Apr 29;358(1432):617-20.
6. Jeneson A, Squire LR. Working memory, long-term memory, and medial temporal lobe function. Learn. Mem. 2012 Jan;19(1):15-25.
7. Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997; 54: 369–76.
8. Zeman AZJ, Boniface SJ, Hodges JR. Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. J Neurol Neurosurg Psychiatry 1998; 64: 435–43.
9. Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, Zeman AZJ. The syndrome of transient epileptic amnesia: Syndrome of TEA. Ann Neurol. 2007 Jun;61(6):587–98.
10. Muhlert N, Grünewald RA, Hunkin NM, Reuber M, Howell S, Reynders H, et al. Accelerated long-term forgetting in temporal lobe but not idiopathic generalised epilepsy. Neuropsychologia. 2011 Jul;49(9):2417–26.

11. Manes F. Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Oct 1;76(10):1387–91.
12. Prueter C Norra C. (2005) Mood disorders and their treatment in patients with epilepsy. J Neuropsychiatry Clin Neurosci 17: 20 – 28.
13. Austin MP ,Ross M, Murray C,O'Carroll RE,Ebmeiers KP, Godwin GM.(1992) Cognitive function in major depression. J Affect Disord 25:21-30.
14. Brown RG,Scott LC, Bench CJ,Dolan RJ. (1994) Cognitive function in depression:its relationship to thebpresene and severity of inellectual decline. Psychol Med 24:829-847.
15. Diamond Klah S, Mohamed A, ThayerZ, (2008) Everyday memory in partial epilepsy: impact of retention and mood. College of clinical Neuropsychologists 14th annual conference. Aust J psychol, pp, 209-226.
16. Oxbury JM, Oxbury SM. Neuropsychology, memory and hippocampal pathology. In: Reynolds EH, Trimble MR, editors. The bridge between neurology and psychiatry. New York: Churchill Livingstone Inc.; 1989.
17. Rausch R, Babb TL. Hippocampal neuron loss and memory scores before and after temporal lobe surgery for epilepsy. Arch Neurol 1993; 50: 812–7.
18. Pauli E, Hildebrandt M, Romstock J, Stefan H, Blumcke I. Deficient memory acquisition in temporal lobe epilepsy is predicted by hippocampal granule cell loss. Neurology 2006; 67: 1383–9.
19. Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. Ann Neurol 1992; 31: 629–37.

20. Kilpatrick C, Murrie V, Cook M, Andrewes D, Desmond P, Hopper J. Degree of left hippocampal atrophy correlates with severity of neuropsychological deficits. Seizure 1997; 6: 213–8.
21. Reminger SL, Kaszniak AW, Labiner DM, Littrell LD, David BT, Ryan L, et al. Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. Epilepsy Behav 2004; 5: 687–95.
22. Dodrill CB. The relationship of neuropsychological abilities to seizure factors and to surgery for epilepsy. Acta Neurol Scand Suppl 1992; 140: 106–10.
23. Giovagnoli AR, Mascheroni S, Avanzini G. Self-reporting of everyday memory in patients with epilepsy: relation to neuropsychological, clinical, pathological and treatment factors. Epilepsy Res 1997; 28: 119–28.
24. Lespinet V, Bresson C, N'Kaoua B, Rougier A, Claverie B. Effect of age of onset of temporal lobe epilepsy on the severity and the nature of preoperative memory deficits. Neuropsychologia 2002; 40: 1591–600.
25. Hendriks MPH, Aldenkamp AP, Alpherts WCJ, Ellis J, Vermeulen J, van der Vlugt H. Relationships between epilepsy-related factors and memory impairment. Acta Neurol Scand 2004; 110: 291–300.
26. Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004; 62: 1736–42.
27. Baxendale SA, Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF, et al. The Relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. Epilepsia 1998; 39: 158–66.

28. Gleissner U, Helmstaedter C, Elger CE. Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1998; 65: 665–9.
29. Dekeyzer S, De Kock I, Nikoubashman O, Vanden Bossche S, Van Eetvelde R, De Groote J, et al. "Unforgettable" – a pictorial essay on anatomy and pathology of the hippocampus. Insights Imaging. 2017 Apr;8(2):199–212.
30. Piazzini A, Canevini MP, Maggiori G, Canger R. The perception of memory failures in patients with epilepsy. Eur J Neurol 2001; 8: 613–20.
31. Fitzgerald Z, Thayer Z, Mohamed A, et al. Examining factors related to accelerated long-term forgetting in epilepsy using ambulatory EEG monitoring. Epilepsia 2013;54:819–27.
32. Tulving E, Schacter DL, McLachlan DR, Moscovitch M. Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. Brain Cogn 1988; 8: 3–20.
33. Kopelman MD, Wilson BA, Baddeley AD (1989) The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. J Clin Exp Neuropsychol **11**:724–744.
34. Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. Psychol Rev 2000; 107: 261–88.n
35. Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21.
36. Maguire EA. 2001. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci 356:1441–1451.

37. Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376–380.
38. Kopelman MD, Stanhope N, Kingsley D. 1999. Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions. Neuropsychologia 37:939–958.
39. Viskontas IV, McAndrews MP, Moscovitch M. 2000. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. J Neurosci 20:5853–5857.
40. Kirwan CB, Bayley PJ, Galvan VV, Squire LR. 2008. Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. Proc Natl Acad Sci USA 105:2676–2680.
41. Addis DR, Moscovitch M, McAndrews MP. 2007a. Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. Brain 130 (Pt 9):2327–2342.
42. Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. Nat Med. 2017 Jun;23(6):678–80.
43. Martin, R. C., Loring, D. W., Meador, K. J., Lee, G. P., Thrash, N., & Arena, J. G. (1991). Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology, 5*(1), 3–12.
44. O'Connor, M., Sieggreen, M. A., Ahern, G., Schomer, D., & Mesulam, M. 1997). Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain and Cognition*, *35*(1), 71-84.

45. Kapur N, Millar J, Colbourn C et al. Very long-term amnesia in association with temporal lobe epilepsy: evidence for multiple-stage consolidation processes. Brain Cogn 1997: 35: 58-70.
46. Blake RV. Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. Brain. 2000 Mar 1;123(3):472–83.
47. Bell, B., Fine, J., Dow, C., Seidenberg, M., & Hermann, B. (2005). Temporal lobe epilepsy and the selective reminding test: The conventional 30-minute delay suffices. Psychological Assessment, 17, 103–109.
48. Bell, B. (2006). WMS-III logical memory performance after a two-week delay in temporal lobe epilepsy and control groups. Journal of Clinical & Experimental Neuropsychology, 28, 1435–1443.
49. Giovagnoli, A. R., Casazza, M., & Avanzini, G. (1995). Visual learning on a selective reminding procedure and delayed recall in patients with temporal lobe epilepsy. Epilepsia, 36, 704–711.
50. Howard, C. E., Andres, P., Broks, P., Noad, R., Sadler, M., Coker, D., et al. (2010). Memory, metamemory and their dissociation in temporal lobe epilepsy. Neuropsychologia, 48(4), 921–932.
51. Mameniskiene, R., Jatuzis, D., Kaubrys, G., & Budrys, V. (2006). The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. Epilepsy & Behavior, 8, 278–288.
52. Wilkinson H, Holdstock JS, Baker G, Herbert A, Clague F, Downes JJ. Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. Cortex. 2012 Mar;48(3):317–32.

53. Noulhiane M, Piolino P, Hasboun D, Clemenceau S, Baulac M, Samson S. Autobiographical memory after temporal lobe resection: Neuropsychological and MRI volumetric findings. Brain 2007; 130: 3184–99.
54. Lucchelli F, Spinnler H. Ephemeral new traces and evaporated remoteengrams: a form of neocortical temporal lobe amnesia? A preliminary case report. Neurocase 1998; 4: 447–59.
55. Voltzenlogel V, Despres O, Vignal J-P, Steinhoff BJ, Kehrli P, Manning L. Remote memory in temporal lobe epilepsy. Epilepsia 2006; 47: 1329–36.
56. Barr WB, Goldberg E, Wassersein J, Novelly R. Retrograde amnesia following unilateral temporal lobectomy. Neuropsychologia 1990; 28: 243–55.
57. Manning L, Chassagnon S, Hirsch E, Kehrli P, Maitrot D. Selective memory impairment for public events in a patient with left temporal lobe epilepsy. Epilepsy Res 2005; 64: 45–7.
58. Butler CR, Bhaduri A, Acosta-Cabronero J, Nestor PJ, Kapur N, Graham KS, et al. Transient epileptic amnesia: regional brain atrophy and its relationship to memory deficits. Brain. 2009 Feb;132(2):357–68.
59. Milton F, Muhlert N, Pindus DM, Butler CR, Kapur N, Graham KS, et al. Remote memory deficits in transient epileptic amnesia. Brain. 2010 May 1;133(5):1368–79.
60. Miller LA, Muñoz DG, Finmore M. Hippocampal sclerosis and human memory. Arch Neurol. 1993 Apr;50(4):391-4.
61. Winston GP, Stretton J, Sidhu MK, Symms MR, Thompson PJ, Duncan JS. Structural correlates of impaired working memory in hippocampal sclerosis. Epilepsia. 2013 Jul;54(7):1143-53.
62. Kapur N, Ellison D,Smith MP, Mc Lellan DL,Burrows EH, Focal retrograd amnesia following bilateral temporal lobe pathology, Brain 1992;115:73-85.

63. Hodges JR,Patterson K,Tyler LK, Loss of semantic memory:implications for the modulatory of mind. Cogn Neuropsychol 1994;11:505-42.
64. Squire LR, Cohen N, Nadel L. The medial temporal lobe and memory consolidation: a new hypothesis. In: Eingertner E, Parker E, editors. Memory consolidation: psychobiology of cognition. Hillsdale, NJ: Lawrence Erlbaum; 1984. p. 185–210.
65. Squire LR, Alvarez P. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 1995; 5: 169–77.
66. Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 1997; 7: 217–27.
67. Isaac CL, Mayes AR. Rate of forgetting in amnesia: I. Recall and recognition of prose. J Exp Psychol Learn Mem Cogn 1999a; 25: 942–62.
68. Jokeit H, Kramer G, Ebner A. Do antiepileptic drugs accelerate forgetting? Epilepsy Behav 2005; 6: 430–2.
69. Lewis P, Kopelman MD. Forgetting rates in neuropsychiatric disorders. J Neurol Neurosurg Psychiatry 1998; 65: 890–8.
70. Bergin PS, Thompson PJ, Baxendale SA, Fish DR, Shorvon SD. Remote memory in epilepsy. Epilepsia 2000; 41: 231–9.
71. Lah S, Grayson S, Lee T, Miller L. Memory for the past after temporaL lobectomy: impact of epilepsy and cognitive variables. Neuropsychologia 2004; 42: 1666–79.
72. Lah S, Lee T, Grayson S, Miller L. Effects of temporal lobe epilepsy on retrograde memory. Epilepsia 2006; 47: 615–25.
73. Ricci M, Mohamed A, Savage G, Boserio J, Miller LA. The impact of epileptiform abnormalities and hippocampal lesions on retention of recent autobiographical experiences: Adding insult to injury? Neuropsychologia. 2015 Jan;66:259–66.

74. Warren Z, Haslam C. Overgeneral memory for public and autobiographical events in depression and schizophrenia. Cogn Neuropsychiatry 2007; 12: 301–21.

75. Butler C, Kapur N, Zeman A, Weller R, Connelly A. Epilepsy-related long-term amnesia: Anatomical perspectives. Neuropsychologia. 2012 Nov;50(13):2973–80.

76. Atherton KE, Filippini N, Zeman AZJ, Nobre AC, Butler CR. Encoding-related brain activity and accelerated forgetting in transient epileptic amnesia. Cortex. 2019 Jan;110:127–40.

77. Audrain S, McAndrews MP. Cognitive and functional correlates of accelerated long-term forgetting in temporal lobe epilepsy. Cortex. 2019 Jan;110:101–14.

78. Beilharz JE, Thayer Z, Nikpour A, Lah S. Accelerated long-term forgetting is not evident in adults with genetic generalized epilepsy irrespective of the paradigm used. Epilepsy & Behavior. 2020 Mar;104:106920.

79. Davidson, M., Dorris, L., O'Regan, M., & Zuberi, S. (2007). Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. *Epilepsy & Behavior, 11*, 394-400. doi: 10.1016/j.yebeh.2007.05.004.

80. Gascoigne MB, Barton B, Webster R, Gill D, Antony J, Lah SS. Accelerated long-term forgetting in children with idiopathic generalized epilepsy: *Accelerated Long-Term Forgetting in Children*. Epilepsia. 2012 Dec;53(12):2135–40.

81. Grayson-Collins J, Gascoigne MB, Barton B, Webster R, Gill D, Lah S. Longitudinal study of accelerated long-term forgetting in children with genetic generalized epilepsy: Evidence of ongoing deficits. Cortex. 2019 Jan;110:5–15.

82. Khwaja GA, Duggal A, Kulkarni A, Chaudhry N, Gupta M, Chowdhury D, Bohra V. Recurrent prolonged fugue states as the sole manifestation of epileptic seizures. Ann Indian Acad Neurol. 2013 Oct;16(4):561-4.

83. Mishra A, Goel RK. Psychoneurochemical investigations to reveal neurobiology of

memory deficit in epilepsy. Neurochem Res. 2013 Dec;38(12):2503-15.

84. Rai VK, Shukla G, Afsar M, Poornima S, Pandey RM, Rai N, Goyal V, Srivastava A, Vibha D, Behari M. Memory, executive function and language function are similarly impaired in both temporal and extra temporal refractory epilepsy-A prospective study. Epilepsy Res. 2015 Jan;109:72-80.
85. Shah U, Desai A, Ravat S, et al. Memory outcomes in mesial temporal lobe epilepsy surgery. *Int J Surg*. 2016;36(Pt B):448-453.
86. Wechsler, D. (1997). Wechsler memory scale III. San Antonio, TX: The Psychological Corporation.
87. Schmidt M. Rey auditory verbal learning test: a handbook. Los Angeles: Western Psychological Services, 1996.
88. Osterreith P, Rey A. Le test de copie d'une figure complexe. Arch Psychol 1944;30:205–220.
89. Miller LA, Mothakunnel A, Flanagan E, Nikpour A, Thayer Z. Accelerated Long Term Forgetting in patients with focal seizures: Incidence rate and contributing factors. Epilepsy & Behavior. 2017 Jul;72:108–13.
90. Contador I, Sánchez A, Kopelman MD, González de la Aleja J. Long-term forgetting in temporal lobe epilepsy: Is this phenomenon a norm? Epilepsy & Behavior. 2017 Dec;77:30–2.
91. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 2006; 44: 2189–208.
92. Matthias Gärtnera, Verena Brodbeck et al, 'A stochastic model for EEG microstate sequence analysis', https://doi.org/10.1016/j.neuroimage.2014.10.014.
93. Hoefeijzers S, Dewar M, Della Sala S, Zeman A, Butler C. Accelerated long-term forgetting in transient epileptic amnesia: An acquisition or consolidation deficit?

Neuropsychologia. 2013 Jul;51(8):1549–55.

94. Cassel A, Morris R, Koutroumanidis M, Kopelman M. Forgetting in temporal lobe epilepsy: When does it become accelerated? Cortex. 2016 May;78:70–84.

APPENDIX

ABBREVIATIONS

ILAE - International League Against Epilepsy

PWE – Persons with epilepsy

TLE - Temporal lobe epilepsy

TEA - Transient epileptic amnesia

LTM - Long-term memory

LTP - Long-term potentiation

MTL – Medial temporal lobe

MTS – Mesial temporal sclerosis

AED – Antiepileptic drug

IGE – Idiopathic generalized epilepsy

ALF - Accelerated long-term forgetting

AA - Autobiographical amnesia

MRI - Magnetic resonance imaging

EEG – Electroencephalogram

IED – Interictal epileptiform discharge

IQ – Intelligence Quotient

VAIS - Verbal Adult Intelligence Scale

WAPIS - Weschler Adult Performance Intelligence Scale

RAVLT - Rey Auditory Verbal Learning Test

RCFT - Rey-Osterrieth Complex Figure Test

AMI - Autobiographical Memory Interview

ATL – Anterior temporal lobectomy

STC – Standard theory of consolidation

MTC – Multiple Trace theory of consolidation

CALL NOTIFICATION FOR HEALTHY VOLUNTEERS

This is to notify that a scientific study is being conducted in SCTIMST, Trivandrum titled "Quantitative Electroencephalogram and Multi-Model Neuro-imaging biomarkers of Memory dysfunction in Epilepsy". This study helps to throw light on memory dysfunction in epilepsy patients and to establish the biomarkers of this dysfunction. This study also includes healthy people for comparison with epilepsy patients. Participation of healthy volunteers in this study involves memory and neuropsychological assessment. Healthy volunteers willing to participate in this study can contact the below mentioned number/person for further details.

Dr. Pavan Kumar Rudrabhatla,

Senior Resident, Dept. of Neurology,

Ph: 9159525608,

Mail: pavankumar@sctimst.ac.in

ആരോഗ്യമുള്ള സന്നദ്ധപ്രവർത്തകർക്കായുള്ള ക്ഷണം

തിരുവനന്തപുരം ശ്രീചിത്രയിൽ ''എപ്പിലെപ്സിയിലെ, ഓർമ്മയുടെ താളംതെറ്റലിന്റെ ഇലക്ട്രോഎൻസഫലോഗ്രാം (ഇഇജി) അളവുകളും, ബഹുമാതൃകാ ന്യൂറോ ചിത്രീകരണ ജൈവസൂചകങ്ങളും'' എന്ന ഒരു ശാസ്ത്രീയ പഠനം നടത്തുന്നതായി അറിയിക്കുന്നു. അപസ്മാരരോഗികളിലെ ഓർമ്മശക്തിയുടെ പ്രവർത്തനരാഹിത്യത്തിൽ വെളിച്ചം വീശുന്നതിനും ഈ പ്രവർത്തനരാഹിത്യത്തിന്റ ജീവസൂചകങ്ങൾ നിർണ്ണയിക്കുന്നതിനുമാണ് ഈ പഠനം. അപസ്മാരരോഗികളുമായി താരതമ്യം ചെയ്യാൻ ആരോഗ്യമുള്ള സന്നദ്ധപ്രവർത്തകരെയും ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തുന്നു. ആരോഗ്യമുള്ല സന്നദ്ധപ്രവർത്തകർ പങ്കെടുക്കുമ്പോൾ അവരുടെ ഓർമ്മശക്തിയുടെയും ന്യൂറോ ഫിസിയോളജിയുടെയും പരിശോധനയും ഉൾക്കൊള്ളുന്നു. പഠനത്തിൽ പങ്കെടുക്കാൻ താത്പര്യമുള്ള ആരോഗ്യമുള്ള സന്നദ്ധപ്രവർത്തകർക്ക് വിശദവിവരങ്ങൾക്കായി താഴെപ്പറയുന്ന വ്യക്തിയെ ബന്ധപ്പെടാം.

ഡോ. പവർകുമാർ രുദ്രഭട്ല

സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്

ഫോൺ. 9159525608

ഇമെയിൽ. pavankumar@sctimst.ac.in

PARTICIPANT PROFORMA

Participant Number:

Participant Name:

Group:

Hospital Number:

Age/Sex:

Education:

Years of education:

Occupation:

Address:

Phone Number:

Age of epilepsy onset:

Duration of epilepsy:

Seizure frequency:

Last attack date:

AEDs (Number and drugs):

Body weight (Kg):

Date of baseline evaluation:

Date of Day-5 evaluation:

Number of events between baseline and 5 days assessment:

Neuropsychology

RAVLT:

RCFT:

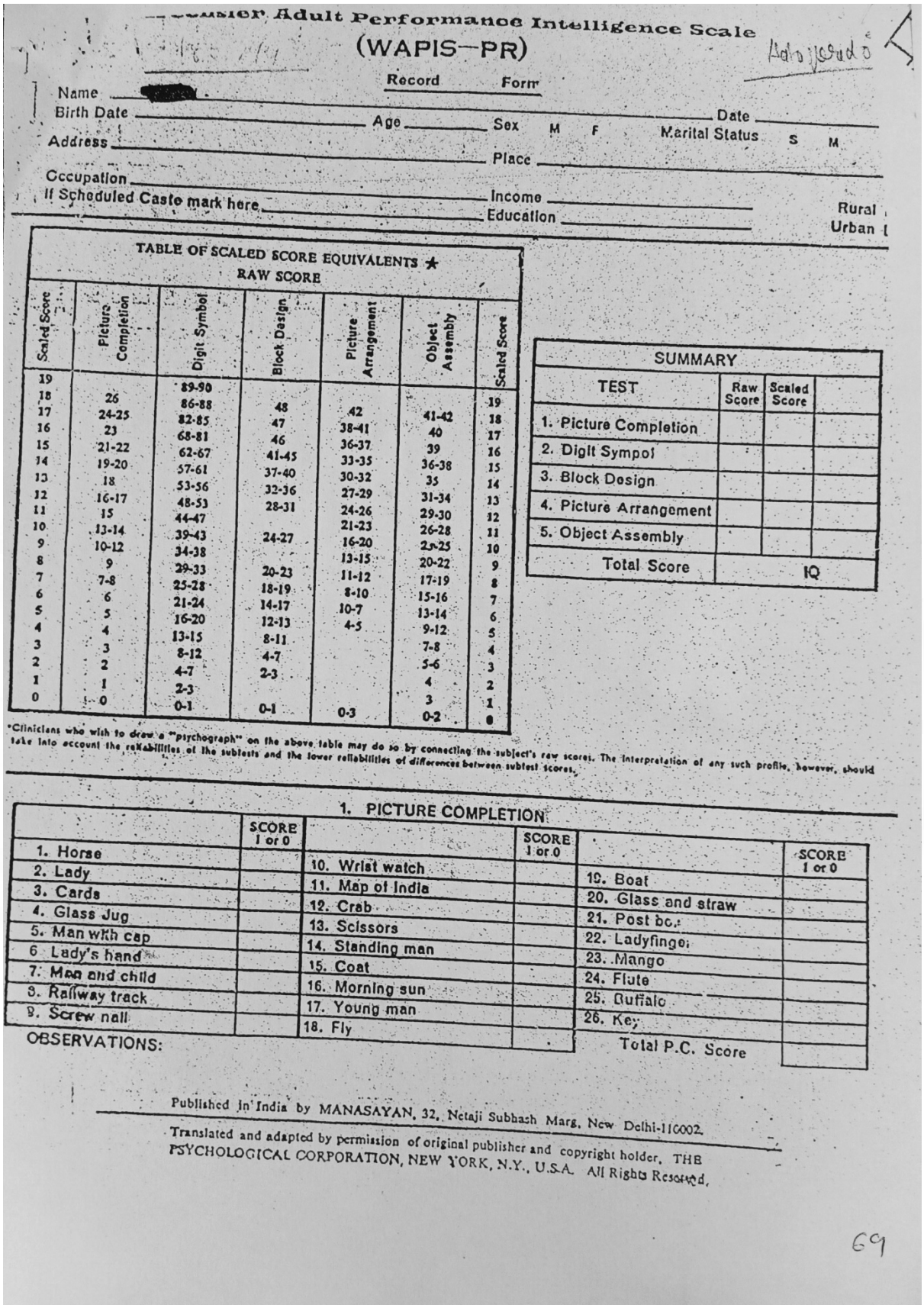
AMI:

EEG findings:

MRI findings:

NEUROPSYCHOLOGICAL TESTS

Wechsler Adult Performance Intelligence Scale (WAPIS)



—Wechsler Adult Performance Intelligence Scale

(WAPIS—PR)

Adolescents

Record Form

Name [redacted]

Birth Date _____ Age _____ Sex M F Date _____

Address _____ Marital Status S M

Place _____

Occupation _____ Income _____

If Scheduled Caste mark here _____ Education _____ Rural / Urban

TABLE OF SCALED SCORE EQUIVALENTS *

Scaled Score	Picture Completion	Digit Symbol	Block Design	Picture Arrangement	Object Assembly	Scaled Score
19		89-90				19
18	26	86-88	48	42	41-42	18
17	24-25	82-85	47	38-41	40	17
16	23	68-81	46	36-37	39	16
15	21-22	62-67	41-45	33-35	36-38	15
14	19-20	57-61	37-40	30-32	35	14
13	18	53-56	32-36	27-29	31-34	13
12	16-17	48-53	28-31	24-26	29-30	12
11	15	44-47		21-23	26-28	11
10	13-14	39-43	24-27	16-20	2n-25	10
9	10-12	34-38		13-15	20-22	9
8	9	29-33	20-23	11-12	17-19	8
7	7-8	25-28	18-19	8-10	15-16	7
6	6	21-24	14-17	10-7	13-14	6
5	5	16-20	12-13	4-5	9-12	5
4	4	13-15	8-11		7-8	4
3	3	8-12	4-7		5-6	3
2	2	4-7	2-3		4	2
1	1	2-3			3	1
0	0	0-1	0-1	0-3	0-2	0

*Clinicians who wish to draw a "psychograph" on the above table may do so by connecting the subject's raw scores. The interpretation of any such profile, however, should take into account the reliabilities of the subtests and the lower reliabilities of differences between subtest scores.

SUMMARY			
TEST	Raw Score	Scaled Score	
1. Picture Completion			
2. Digit Sympol			
3. Block Design			
4. Picture Arrangement			
5. Object Assembly			
Total Score		IQ	

1. PICTURE COMPLETION

	SCORE 1 or 0		SCORE 1 or 0		SCORE 1 or 0
1. Horse		10. Wrist watch		19. Boat	
2. Lady		11. Map of India		20. Glass and straw	
3. Cards		12. Crab		21. Post box	
4. Glass Jug		13. Scissors		22. Ladyfinger	
5. Man with cap		14. Standing man		23. Mango	
6 Lady's hand		15. Coat		24. Flute	
7. Man and child		16. Morning sun		25. Buffalo	
8. Railway track		17. Young man		26. Key	
9. Screw nail		18. Fly		Total P.C. Score	

OBSERVATIONS:

Published in India by MANASAYAN, 32, Netaji Subhash Marg, New Delhi-110002.

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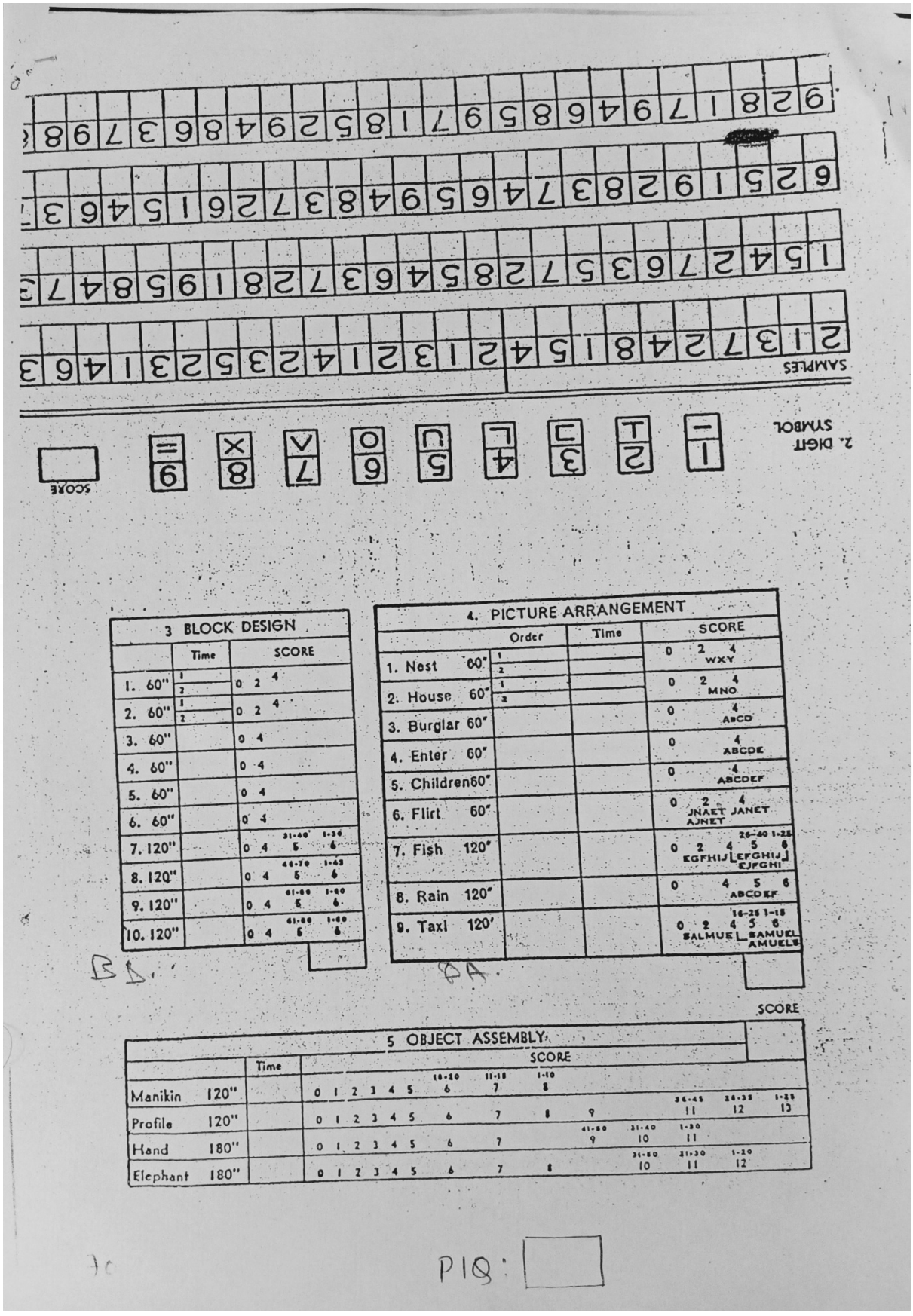
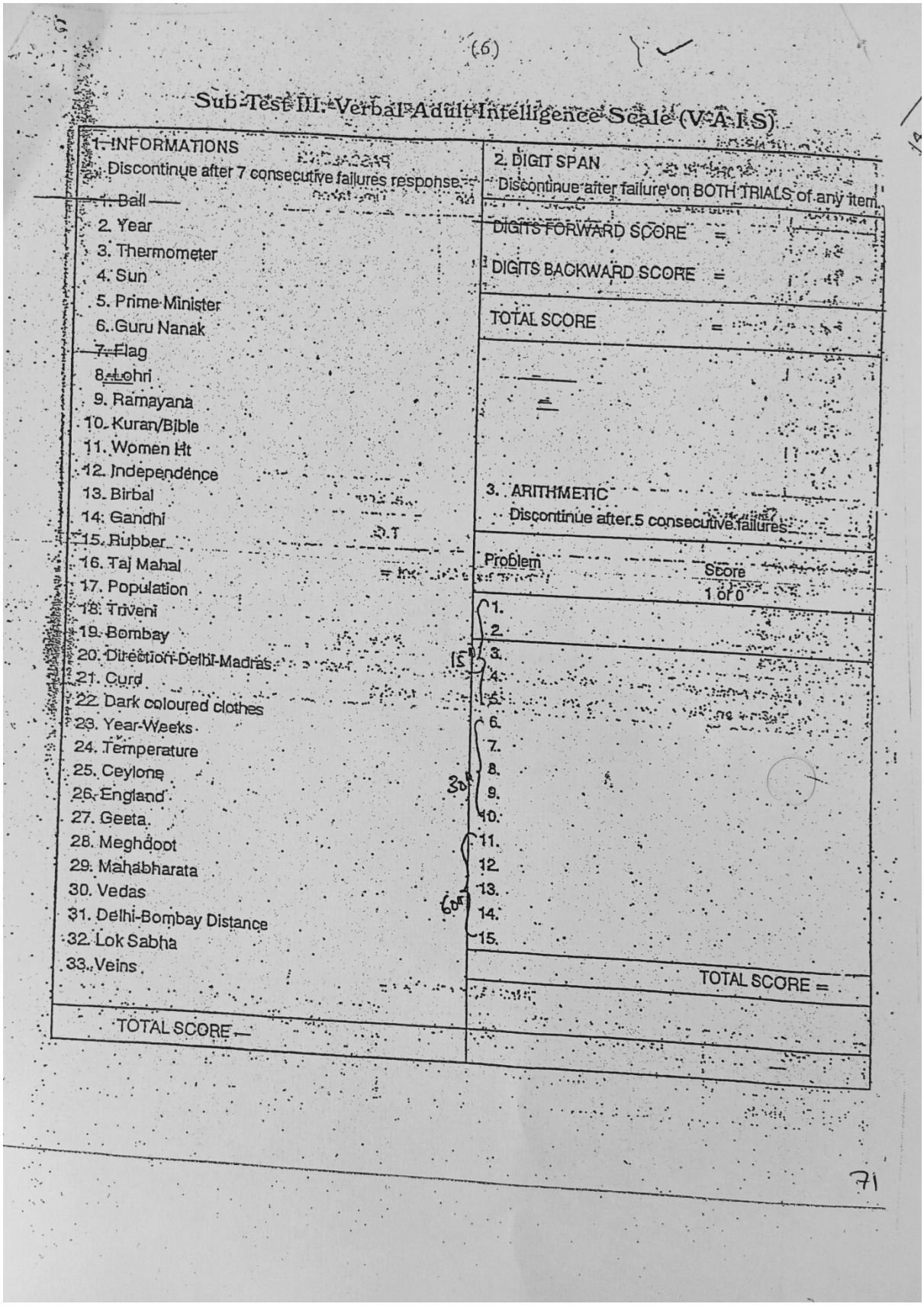

SAMPLES
2. DIGIT SYMBOL
SCORE
3 BLOCK DESIGN
Time
SCORE
1. 60"
2. 60"
3. 60"
4. 60"
5. 60"
6. 60"
7. 120"
8. 120"
9. 120"
10. 120"
4. PICTURE ARRANGEMENT
Order
Time
SCORE
1. Nest 60"
2. House 60"
3. Burglar 60"
4. Enter 60"
5. Children 60"
6. Flirt 60"
7. Fish 120"
8. Rain 120"
9. Taxi 120'
WXY
MNO
ABCD
ABCDE
ABCDEF
JNAET AJNET JANET
EGFHIJ EJFGHI EFGHIJ
ABCDEF
SALMUEL SAMUEL AMUELS
5 OBJECT ASSEMBLY
Time
SCORE
Manikin 120"
Profile 120"
Hand 180"
Elephant 180"

Verbal Adult Intelligence Scale (VAIS)



(6)

Sub-Test III: Verbal Adult Intelligence Scale (V.A.I.S)

1. INFORMATIONS
Discontinue after 7 consecutive failures response

1. Ball
2. Year
3. Thermometer
4. Sun
5. Prime Minister
6. Guru Nanak
7. Flag
8. Lohri
9. Ramayana
10. Kuran/Bible
11. Women Lit
12. Independence
13. Birbal
14. Gandhi
15. Rubber
16. Taj Mahal
17. Population
18. Triveni
19. Bombay
20. Direction-Delhi-Madras
21. Curd
22. Dark coloured clothes
23. Year-Weeks
24. Temperature
25. Ceylone
26. England
27. Geeta
28. Meghdoot
29. Mahabharata
30. Vedas
31. Delhi-Bombay Distance
32. Lok Sabha
33. Veins

TOTAL SCORE

2. DIGIT SPAN
Discontinue after failure on BOTH TRIALS of any item

DIGITS FORWARD SCORE =

DIGITS BACKWARD SCORE =

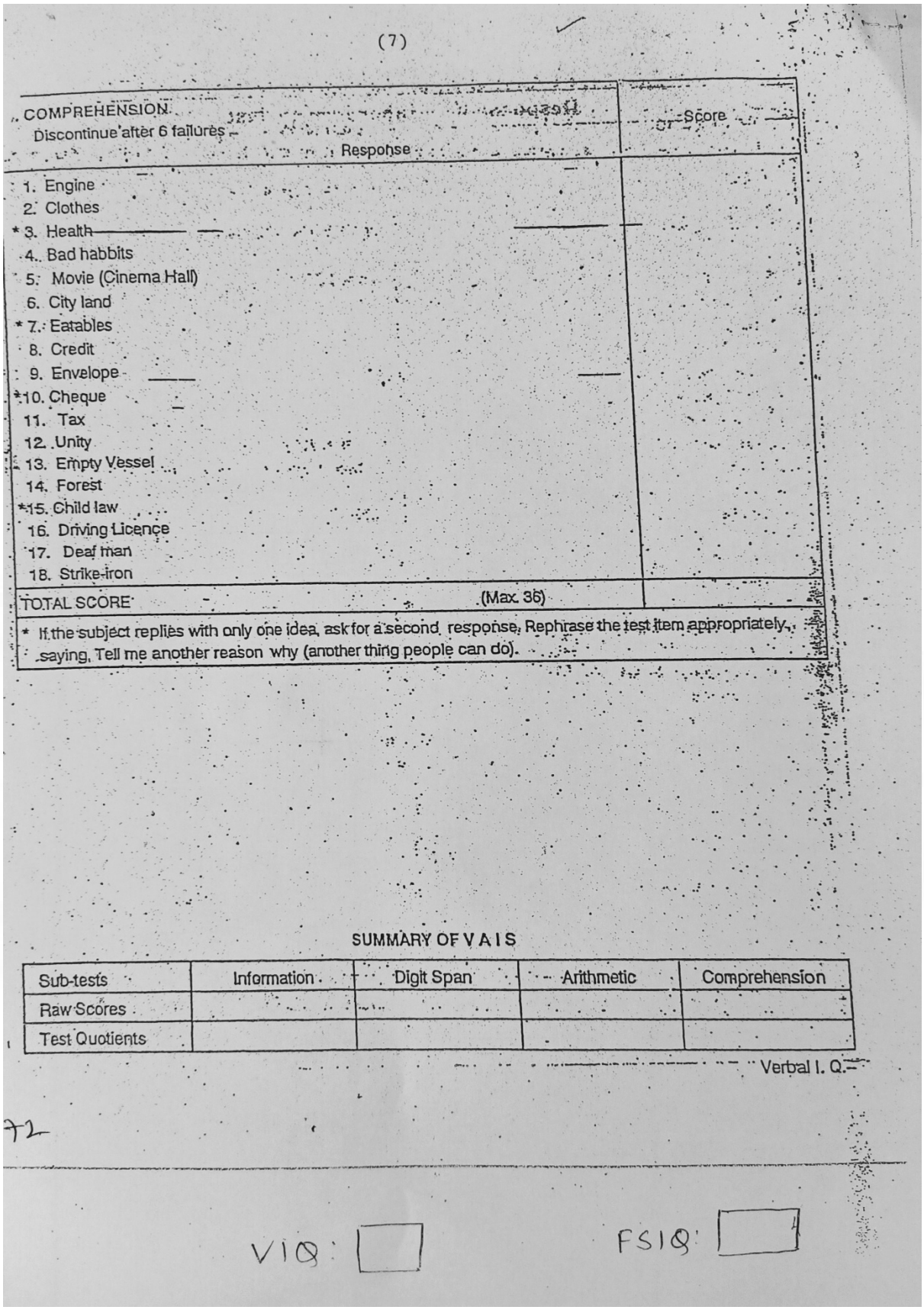
TOTAL SCORE =

3. ARITHMETIC
Discontinue after 5 consecutive failures

Problem	Score 1 or 0
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	
13.	
14.	
15.	

TOTAL SCORE =

71



(7)

COMPREHENSION Discontinue after 6 failures	Response	Score
1. Engine		
2. Clothes		
* 3. Health		
4. Bad habbits		
5. Movie (Cinema Hall)		
6. City land		
* 7. Eatables		
8. Credit		
9. Envelope		
*10. Cheque		
11. Tax		
12. Unity		
13. Empty Vessel		
14. Forest		
*15. Child law		
16. Driving Licence		
17. Deaf man		
18. Strike-iron		
TOTAL SCORE	(Max. 36)	

* If the subject replies with only one idea, ask for a second response, Rephrase the test item appropriately, saying, Tell me another reason why (another thing people can do).

SUMMARY OF V A I S

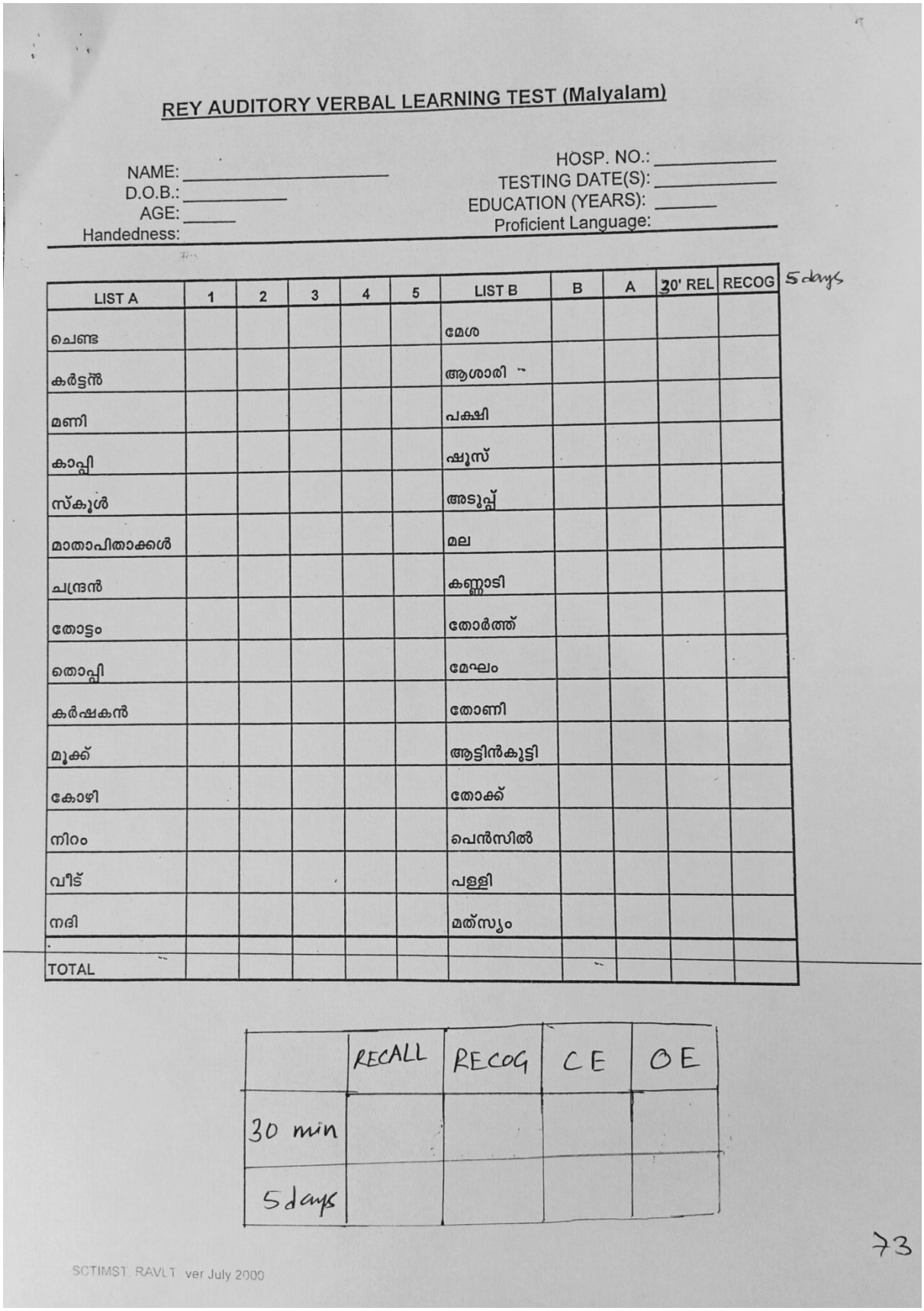
Sub-tests	Information	Digit Span	Arithmetic	Comprehension
Raw Scores				
Test Quotients				

Verbal I. Q.

72

VIQ: FSIQ:

Rey Auditory Verbal Learning Test (RAVLT)



REY AUDITORY VERBAL LEARNING TEST (Malyalam)

NAME: _____ HOSP. NO.: _____
D.O.B.: _____ TESTING DATE(S): _____
AGE: _____ EDUCATION (YEARS): _____
Handedness: _____ Proficient Language: _____

LIST A	1	2	3	4	5	LIST B	B	A	20' REL	RECOG
ചെണ്ട						മേശ				
കർട്ടൻ						ആശാരി				
മണി						പക്ഷി				
കാപ്പി						ഷൂസ്				
സ്കൂൾ						അടുപ്പ്				
മാതാപിതാക്കൾ						മല				
ചന്ദ്രൻ						കണ്ണാടി				
തോട്ടം						തോർത്ത്				
തൊപ്പി						മേഘം				
കർഷകൻ						തോണി				
മൂക്ക്						ആട്ടിൻകുട്ടി				
കോഴി						തോക്ക്				
നിറം						പെൻസിൽ				
വീട്						പള്ളി				
നദി						മത്സ്യം				
TOTAL										

5 days

	RECALL	RECOG	CE	OE
30 min				
5 days				

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SCTIMST. RAVLT ver July 2000

RAVLT DELAYED RECOGNITION TRIAL FOR FORM A (Malyalam) (30mn)

Instructions: Read the following words and ask the patient to **respond 'yes' or 'no' to each word that is read out, according to whether you think the word was on list A**. Circles every word that has a 'yes' response.

മണി	a	ഭവനം	sa	തോർത്ത്	b	തോണി	b	കണ്ണാടി	b
ജനൽ	sa	മത്സ്യം	b	കർട്ടൻ	a	തപ്പി	pa	സോക്സ്	sb
തൊപ്പി	a	ചന്ദ്രൻ	a	പൂവ്	sa	മാതാപിതാക്കൾ	a	ഷൂസ്	b
ധാന്യപ്പുര	sa	തോഴി	pa	നിറം	a	വെള്ളം	sa	അദ്ധ്യാപകൻ	sa
ആശാരി	b	ഇന്ദ്രൻ	pa	മേശ	b	കർഷകൻ	a	അടുപ്പ്	b
മൂക്ക്	a	പക്ഷി	b	തോക്ക്	b	തൂക്ക്	sa	കൂട്	pa
കാലാവസ്ഥ	sb	മല	b	കളർപെൻസിൽ	sa	മേഘം	b	കുട്ടികൾ	sa
സ്കൂൾ	a	കാപ്പി	a	പള്ളി	b	വീട്	a	ചെണ്ട	a
കുപ്പി	pa	വീണ	pa	കോഴി	a	മൂശാരി	pb	കാച്ചി	pa
പെൻസിൽ	b	നദി	a	തല	pb	തോട്ടം	a	ആട്ടിൻകുട്ടി	b

key

a	list A words
b	list B words
s	words with a semantic association to a word on list A or B
p	words phonemically similar to a word on list A or B

RAVLT DELAYED RECOGNITION TRIAL FOR FORM A (Malyalam) (5 days)

Instructions: Read the following words and ask the patient to **respond 'yes' or 'no' to each word that is read out, according to whether you think the word was on list A**. Circles every word that has a 'yes' response.

മണി	a	ഭവനം	sa	തോർത്ത്	b	തോണി	b	കണ്ണാടി	b
ജനൽ	sa	മത്സ്യം	b	കർട്ടൻ	a	തപ്പി	pa	സോക്സ്	sb
തൊപ്പി	a	ചന്ദ്രൻ	a	പൂവ്	sa	മാതാപിതാക്കൾ	a	ഷൂസ്	b
ധാന്യപ്പുര	sa	തോഴി	pa	നിറം	a	വെള്ളം	sa	അദ്ധ്യാപകൻ	sa
ആശാരി	b	ഇന്ദ്രൻ	pa	മേശ	b	കർഷകൻ	a	അടുപ്പ്	b
മൂക്ക്	a	പക്ഷി	b	തോക്ക്	b	തൂക്ക്	sa	കൂട്	pa
കാലാവസ്ഥ	sb	മല	b	കളർപെൻസിൽ	sa	മേഘം	b	കുട്ടികൾ	sa
സ്കൂൾ	a	കാപ്പി	a	പള്ളി	b	വീട്	a	ചെണ്ട	a
കൂപ്പി	pa	വീണ	pa	കോഴി	a	മൂശാരി	pb	കാച്ചി	pa
പെൻസിൽ	b	നദി	a	തല	pb	തോട്ടം	a	ആട്ടിൻകുട്ടി	b

key

a	list A words
b	list B words
s	words with a semantic association to a word on list A or B
p	words phonemically similar to a word on list A or B

75

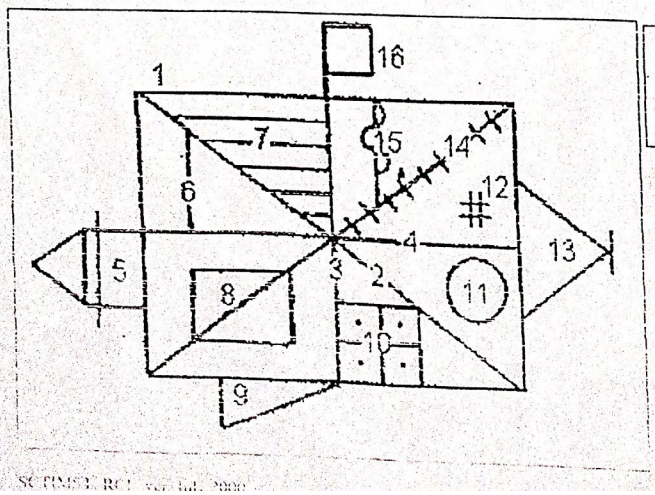
Rey Complex Figure Test (RCFT)

REY COMPLEX FIGURE

Scoring for each of the sixteen elements stated below.

Element is	Placed Poorly	Placed Properly
Correct	1.0	2.0
Distorted or Incomplete	0.5	1.0
Absent or Not Recognisable	0	-

	Elements of the Rey Complex Figure	T1	T2	T3	De	Co
1	Large Rectangle					
2	Diagonal Cross					
3	Vertical Midline					
4	Horizontal Midline					
5	Left Picture including the Vertical Line					
6	Small Vertical Line in Upper Left Quadrant					
7	Five Parallel lines in Upper Left Quadrant					
8	Smaller Rectangle in Lower Left Quadrant					
9	Small Triangle below the Lower Left Quadrant					
10	Small Square with Four Dots in Lower Right Quadrant					
11	Small Circle in Lower Right Quadrant					
12	Hash Symbol in Upper Right Quadrant					
13	Small Triangle with a Small Vertical Line on the Right Side					
14	Nine Small Parallel Lines in Upper Right Quadrant					
15	Vertical and Curved lines in the Upper Right Quadrant					
16	Flag on Top					
	TOTAL SCORE (Max. = 32) =					



*delayed recall is after _____ minutes.

ETHICS COMMITTEE APPROVAL LETTER

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1332/FEBRUARY-2019

25.06.2019

Dr. Sanjeev V Thomas
Senior Professor
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Sanjeev V Thomas,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "QUANTITATIVE ELECTROENCEPHALOGRAM AND MULTI-MODEL NEURO-IMAGING BIOMARKERS OF MEMORY DYSFUNCTION IN EPILEPSY (IEC/1332)" on 16th February, 2019.

The following documents were reviewed:

Original submission

1. *Covering Letter addressed to the Chairman, IEC, SCTIMST with checklist*
2. *Copy of a letter addressed to the Director, SCTIMST dated 8.01.2018 from Dr. Sanjeev V Thomas, Professor, Department of Neurology, SCTIMST*
3. *TAC Approval Letter 4. IEC Application Form 5. Project Proposal 6. Proforma*
7. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST with checklist*
2. *Copy of a letter addressed to the Director, SCTIMST dated 8.01.2018 from Dr. Sanjeev V Thomas, Professor, Department of Neurology, SCTIMST*
3. *TAC Approval Letter 4. IEC Application Form 5. Project Proposal 6. Proforma*
7. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co-Principal Investigators*

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The following members of the Ethics Committee were present at the meeting held on 16th February, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
8.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
9.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
10.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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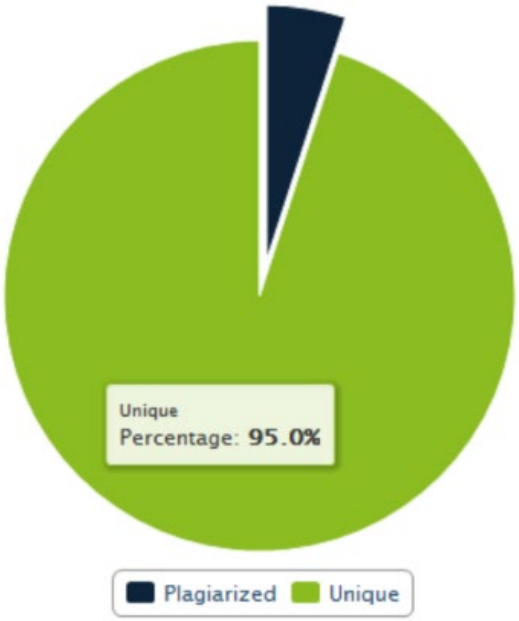

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