

Research Article

Frontal Lobe Dysfunction in Chronic Mesial Temporal Lobe Epilepsies

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Abstract

Background: Chronic mesial temporal lobe epilepsy patients are known to be associated with dysfunction of visual and verbal memory. Recent studies have shown that executive dysfunction which is present in these patients demonstrates existence of abnormality beyond the site of involvement.

Aim: To see whether there is evidence of executive dysfunction in patients with temporal lobe epilepsy and whether it has any correlation with variables like age of onset, duration of illness, number of antiepileptic drugs, side of lesion and seizure frequency.

Materials and Methods: 126 consecutive patients who fulfilled the criteria for unilateral chronic mesial temporal lobe epilepsy after detailed evaluation are taken into study. Detailed neuropsychological assessments like Intelligence Quotient, verbal and visual memory in addition to extensive tests of frontal dysfunction are done.

Results: All tests of executive function have shown statistically significant dysfunction. Age of onset, number of AEDs, duration of illness, seizure burden are seem to have an effect on the executive function. Quality of life is negatively correlated with tests of planning and working memory.

Conclusion: Evidence for frontal lobe dysfunction noted in mesial temporal lobe epilepsies. Mesial temporal lobe epilepsy has effects beyond temporal lobe suggesting the effect of epilepsy on networks. Age of onset, number of AED, duration of illness, side of lesion, seizure frequency seem to have an effect on the executive function. Tests of planning, working memory are correlated with poor quality of life.

Keywords: Frontal lobe dysfunction; Chronic mesial temporal lobe epilepsy; Executive functions; Quality of life

Introduction

Mesial temporal lobe epilepsy (MTLE) patients are the patients with refractory seizures that are not responding to usual antiepileptic therapy in most of the cases. They are found to have febrile seizures or febrile status epilepticus in early childhood (30-40% of them) and after latent period of few years used to develop refractoriness. They are characterized by typical MRI Brain lesion suggestive of sclerosis and atrophy and loss of interdigitations of amygdala, hippocampus and para hippocampal gyrus. Neuropsychological impairment is an important comorbidity of chronic epilepsy especially for temporal lobe epilepsy. Chronic MTLE patients are found to have problems with visual and verbal memory and emotional cognition in concordance to structural abnormalities of amygdala and hippocampus [1]. Frontal lobe function which is thought to be high level function in the cognitive process like decision making, planning, working memory, executive skills are thought to be necessary for day to day life activities. Initially it is thought that frontal lobe functions are spared in temporal lobe epilepsy. Later it is challenged by other studies with emerging evidence of involvement of frontal processes in temporal lobe epilepsy. Functional abnormalities in MTLE may extend beyond the temporal lobes. This fact has also been noted as in PET CT scan Brain where hypometabolic changes have been

extended beyond mesial temporal lobe including lateral temporal areas, prefrontal cortex and in sub cortical structures like thalamus and basal ganglia which are also involved in cognitive functions such as set shifting, planning [2]. Working memory is part of frontal lobe function that has primary role in cognitive processing of the storage and manipulation of information temporarily, whose dysfunction leads to impairment of daily activities including reading a newspaper or following a conversation. The working memory system is supposed to involve subsystems that have bidirectional flow of information between frontotemporal pathways. This is supported by the evidence from psychiatric and neuro degenerative disorders that have temporal lobe involvement in frontal lobe disorders. There is also evidence of disruption of frontotemporal connectivity leading to executive dysfunction [3-7]. Most of the processing deficiencies that are involving executive functions of frontal lobe dysfunction are vital cognitive processes that lead to learning difficulties, social dysfunction that effect lack of employment. This may lead to even worse outcomes in daily living and difficulty in rehabilitation of these patients [7]. The nature and extent of extra temporal involvement in temporal lobe epilepsy is not fully understood. In temporal lobe epilepsy, the frontal lobe impairment is due to either extensive temporal lobe involvement or secondary to propagation of epileptic activity to frontal lobe [8].

Table 1: Demographic Characteristics.

Age	Mean \pm SD: 28.42 \pm 9.4 yrs
Gender	Male 78 (61.9 %) Female 48 (38.1 %)
Education	CE 66(50.65 %), SE 49 (38.8%), UE 11 (8.73 %)
Diagnosis	Right 71 (56.34 %) Left 55 (43.65 %)
Age of onset	<10 yrs-24(31.17 %) 10-20yrs-29 (37.66%) > 20 yrs-24 (31.17 %)
Duration of illness	\leq 10 yrs-38 (49.35 %) 10-20 yrs- 23 (29.87%) >20 yrs-16 (20.78%)
Family history	Present – 18 (23.38%), Absent- 59 (76.62 %)
Number of AEDS	1 -2 -48(62.34%) 3-5 -29(37.66 %)
Handedness	76 right handed (98.70%)
Seizure frequency*	< 6 = 15 (19.48%) \geq 6 = 62 (80.52%)
QOLIE	37(61.53 %)– Poor

*Engel score

Identification of the mechanism of derangement helps to manage the TLE patients by addressing root cause. Recently there are studies which are focused on this aspect. However some studies have reported reduced performance in executive function for MTLE patients as compared with controls whereas other studies have found that there are no relevant differences between patients and controls(). There is no uniformity in the frontal tests used for various studies. There are not many studies which have shown the relation of frequency of seizures or seizure burden on executive dysfunction.

Aims and Objectives

The aim of the study include the following

1. To evaluate frontal lobe dysfunction in mesial temporal lobe epilepsies.
2. To evaluate the effect of age of onset, duration of illness, number of antiepileptic drugs, side of lesion, seizure burden on the frontal lobe function of these patients.

Materials and Methods

126 patients with unilateral MTLE attending epilepsy clinic of department of Neurology in Nizam's Institute of Medical Sciences are taken into study. After detailed clinical and neurological examination, prolonged video-EEG monitoring and detailed neuropsychological examination is done. High-resolution (1.5Tesla/3Tesla) Magnetic Resonance Imaging MRI Brain with epilepsy protocol is done to determine the side of lesion. MTLE is determined in MRI brain by presence of loss of volume (atrophy) and loss of interdigitations and grey -white matter junction differentiation and hyper intensity in T2 in hippocampus. (Abrahams) Side of lesion was analyzed by MRI Brain and detailed history with lateralizing signs. History in addition to prolonged video EEG monitoring which was done for at least 12 hours and if possible seizures are recorded in order to identify the side of lesion. After taking detailed clinical examination along with demographic data and clinical history like age of onset, duration of illness, frequency of seizures, maximum remission period for the seizures, no of AEDs used, family history, birth history are taken. An extensive neuropsychological test battery for executive function

is used. All patients had undergone detailed neuropsychological examination including tests for co-morbidities like depression with Hamilton (HAM- D) and QOLIE – 31 to determine the quality of life. Written informed consent is taken from all patients. Various tests of neuropsychological assessment are done that include assessment of Intelligent Quotient (Wechsler's Adult Intelligent Scale III), assessing learning and memory-verbal memory (Rey's Auditory Verbal Learning Test), Visual memory (Rey complex figure test) and various tests of executive function. Various domains of executive functions are tested by the following tests. Attention is by Digit span (digit forward & digit backward), Fluency by (Phonemic and Categorical fluency), Set shifting and perseveration is by Wisconsin's Card Sorting Test, Working memory is by verbal and visual N back, psychomotor speed & cognitive flexibility by Trail Making Test A & B, Response inhibition is by Stroop effect, Planning is by Tower of London. All these tests are done in all patients. Planning has been defined as the identification and organization of the steps and elements needed to carry out an intention or achieve a goal (Lezak, 1995). This is best evaluated by Tower of London. In this test, the Subject is presented with a goal state of the arrangement of the 3 balls on one of the boards, which is placed near the examiner. The arrangement of the balls in the other board is the initial state. This board is placed near the subject has to arrive at the goal state in the board placed on his side. This can be done with a minimum of 2 moves (2 moves problems), 3moves (3 moves problems), 4 moves (4 moves problems) and 5 moves (5 moves problems). The test commences with the simple level i.e. the 2 moves problems. This is followed by the 3 moves, 4 moves and 5 moves problems in that order. From the task done by patient, mean time to solve the problem, mean number of moves, number of problems solved with the minimum number of moves and overall score of the total number. Set shifting ability is tested using the Wisconsin card sorting test (Milner, 1963). This test examines concept formation, abstract reasoning and the ability to shift cognitive strategies in response to changing environments. The test consists of 128 cards each card is a square of dimensions 8cms by 8cms. Stimuli of various forms are printed on the cards. The stimuli vary in terms of three attributes: color, form and number. The stimuli are geometrical figures of different forms (triangle, star, cross, circle) in different colors (red, green, yellow, blue) and in different numbers (one, two, three, four) which are presented on each card. The deck of 128 cards is arranged according to the sequence of presentation in the test manual and is placed to the left of the subject. The subject is instructed to study the cards and match each successive card from the pack to one of the four stimulus cards. This subject is told only whether each response is right or wrong and is never told the correct sorting principle. The subject has to guess the concept based on the examiner's feedback and continue with the test. Each time the subject places a card if it is according to the principle of sorting in operation at the time, the examiner puts a number on the scoring form starting from the numbers are put in serial order for consecutive correct responses. After the subject places 10 consecutive cards correctly, the tester changes the concept without the subject's knowledge. The subject's capacity to form a mental set is measured by how quickly he/she attains the concept and retains it for 10 consecutive trials. The subject's capacity to perceive a change in the concept when the next sorting principle is introduced is a measure of the set shifting ability. The test is terminated after the subject attains all the 6 concepts or

Table 2: Executive tests in patients with controls.

Neuropsychological test	Patients (Mean±SD)	Normative data(Mean±SD)	P value
Digit Span			
Digit forward	4.25± 1.16	7.00±0.00	t=20.82;p<0.001*
Digit backward	3.51± 1.24	5.00±0.00	t=10.55;p<0.001*
Fluency			
Phonemic	4.62±2.28	9.60±2.96	t=11.70;p<0.001*
Categorical	5.93±3.35	13.49±2.11	t=16.73;p<0.001*
WCST			
No.of Correct Responses	40.74±13.21	69.80±5.09	t=17.726;p<0.001*
Conceptual Level Responses	25.62±12.62	56.17±11.45	t=15.73;p<0.001*
Percentage of Conceptual Level Responses	20.51±10.62	54.26±14.11	t=16.76;p<0.001*
Percentage of Perseverative errors	25.63±14.56	18.90±7.73	t= 3.58;p=0.0005*
No. of categories completed	1.78±1.08	8.62±12.97	t=4.60;p<0.001*
TMT-A	80.97±30.20	57.94±25.10	t=5.045;p<0.001*
TMT-B	118.46±53.60	146.68±71.51	t=2.72;p<0.007*
Stroop effect	176.48±84.78	130.75±46.15	t=4.097;p<0.001*
Tower of London Planning			
2 MT 2MM	34.28±23.51 7.51±4.18 ;	7.48±1.88 2.46±0.26	t=9.967;p<0.001* t=10.57;p<0.001*
3MT 3MM	48.51±27.93; 13.32±4.70	13.41±2.80 3.89±0.28	t=10.97;p<0.001* t=17.57;p<0.001*
4MT 4 MM	62.04±33.73; 22.27±12.46	21.15±3.95 6.68±0.26	t=10.565;p<0.001* t=10.99;p<0.001*
5MT 5 MM	76.43±37.74; 29.71±6.76	23.37±5.03 7.87±0.209	t=12.23;p<0.001* t=28.32;p<0.001*
N Back Verbal			
1 back hits	6.56±1.49	8.39±0.63	t=9.93;p<0.001*
2 back hits	5.62±1.65	6.86±0.69	t=6.05;p<0.001*
1 back errors	5.70±2.29	5±1.23	t=13.72;p<0.001*
2 back errors	5.64±2.15	3.67±1.34	t=6.86;p<0.001*
Visual 1 back hits	6.06±1.72	7.59±0.59	t=7.32;p<0.001*
2 back hits	4.78±1.79	5.95±0.48	t=5.54;p<0.001*
1 back errors	6.39±1.70	3.84±1.05	t=1.115;p<0.001*
2 back errors	6.89±2.88	8.04±1.25	t=1.80;p<0.001*
RAVLT			
TOT	40.10±8.62	55.02±5.41	t=12.85;p= 8.465
IR	6.93±2.73	12.21±1.23	t=15.45;p<0.001*
DR	6.29±3.19	12.23±1.32	t= 15.11;p<0.001*

*Statistically significant.

after all the 128 cards have been used. Ambiguous & unambiguous responses, perseverative & non-perseverative errors are recorded. Response inhibition measures the ease with which a perceptual set can be shifted both to conjoin the changing demands and by suppressing a habitual response in favor of an unusual one. The prefrontal areas are essential for response inhibition. For this the procedure is that stimulus sheet is placed in front of the subject. The subject is asked to ready the stimuli column-wise as fast as possible. The time taken to read all the 11 columns is noted down. Next, the subject is asked to name the color in which the word is printed. This time also the subject proceeds column wise. The time taken to name all the colors is noted down. The words are presented in the mother tongue of the subject. The color names “Blue”, “Green”, “Red” and “Yellow” are printed in capital letters on a paper. The color of the print occasionally corresponds with the color designated by the word. The words are printed in 16 rows and 11 columns. Verbal Working memory N Back Test will be done by presenting thirty randomly consonants common to multiple Indian languages auditorily at the rate of one per second. Nine of the 30 consonants are repeated. The consonants which are repeated are randomly chosen. In the 1 back

test the subject response whenever a consonant is repeated consonant is repeated consecutively. In the 2 back tests the subject responds whenever consonant is repeated after an intervening consonant. The consonants used in the 1 back and the 2 back versions are given in the appendix. Visual working memory was tested using N back test with 1back and 2 back versions. It consisted of 36 cards each of which had one back dot placed randomly along a circle imagined to on the card. The dimensions and location the imaginary circle on each remained constant in all cards. Each card was individually presented to subject. The subject was told to respond whenever the location of dot repeated itself. In the 1 back test, she/he was told to respond whenever the location of the dot was repeated after one intervening card. The number of hits and errors in each test formed the score.

Those patients who are having the following are excluded from study.

Exclusion criteria

1. Patients on antianxiety drugs and antidepressants.
2. Seizures within 48 hours prior to cognitive assessment.

3. Patients with IQ below 70 are excluded from study.
4. Patients with pseudo seizures.

Statistical analysis

Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in number and percentages (%). The power of the study is 76 patients. We included 126 patients as the results are lying within normative data which is detected by using the SPSS, Analysis of variance (ANOVA) has been used to find the significance of study parameters between groups of patients. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Comparison with normative Data which is age, sex & literacy matched is done with in relation to NIMHANS neuropsychology Battery, 2004. Correlations with outcome variables was done with age of onset, duration of illness, number of AEDs, side of lesion and seizure burden with ANOVA and chi-square test. Multiple logistic regression is done to know whether any single test will detect t he executive dysfunction or not. The Statistical software - SAS 9.2, SPSS IBM version 20.0, Stata 10.1, MedCalc9.0.1, Systat 12.0 are used for above calculations.

Results

Out of 126 patients, males are 78 (61.90%) whereas females are 48 (38.1%).The mean age of presentation is 28.42 ± 9.40 years (ranging from16-61 years). Out of them most are i.e, 52.38% are college educated (66/126), 38.8% are school educated those who completed high school (49) and 8.73% are uneducated [11]. Most of them are right handed (98.41%) whereas only two patients are left sided. Right sided MTLE is seen in71 (56.34%) &left sided in 55(43.65%). Mean duration of illness is Family history is seen in 23.38%. Most of them are refractory cases requiring polytherapy (37.66%) and with seizure frequency of Engel score >6 in 80.52%. Overall average quality of life as measured by QOLIE 32 is poor in 61.53% (Table 1). When compared the results of extensive executive battery of tests in comparison with normative data of Indian standard battery NIMHANS Battery of tests, there is statically significant difference with various domains of following tests like Digit span (digit forward & digit backward), Phonemic and Categorical fluency, Wisconsin’s Card Sorting Test, verbal and visual N back, Trail Making Test A & B, Stroop effect and Tower of London that is depicted in Table 2 indicating that there is statistically significant difference in all domains of executive dysfunction. Various domains of executive function are compared with age of onset, duration of illness, frequency of seizures, side of lesion, number of AEDs On univariate analysis, it is found that each test of executive function when compared with the above parameters found to have the following results depicted in the Table 3. Age of onset correlated with Digit backward TMT-A, TMT-B, verbal 2 back errors Visual N back 2 error, 1 move of Tower of London. Duration of illness correlated with TMTA&TMT B, 3&5 moves of Tower of London, Verbal N back 1hits & Visual N back 2 errors. Side of lesion correlated with Digit forward & Digit backward, 3&4 moves of Tower of London. Seizure burden is correlated with Digit forward, Categorical fluency, all domains of WCST , Verbal 1&2 hits & Errors, Visual 1& 2 Hits &errors, TMT –B, 2, 3&4 moves of tower of London and IQ of the patients . Number of AEDs is correlated with categorical fluency,

Table 3: Correlation of Variables with various neuropsychology tests.

Variable	Neuropsych test	P value
Age of onset	DB	P=0.0204*
	TMTA	P=0.00001*
	TMTB	P=0.0009*
	Verbal 2 back	P=0.05*
	VISUAL N BACK 1 ERROR	P=0.04*
	Tower of London(I move)	P=0.005*
Number of AEDS	VISUAL 2 HITS	p= 0.0135*
	CATERGORICAL FLUENCY	p=0.0354*
	Tower of London	
	2 moves	p=0.005*
	5 moves	p=0.043*
	Quality of life	p=0.04*
Duration of illness	IQ	p=0.03*
	DF	p= 0.060**
	TMTA	p= 0.0477*
	TMTB	P=0.005*
	TOWER OF LONDON	p= 0.0546*
	1 move	p= 0.0003*
	3-MOVES	p= 0.0936*
	5-MOVES	p= 0.004**
	VISUAL N BACK 1 ERROR	P=0,05*
	VERBAL N BACK 2 ERROR	p=0.05*
RAVLT –IR	p= 0.010*	
Side of lesion	DR	
	DF	P=0.064
	DB	P=0.01
	3moves	P=0.06
	4 moves	P= 0.03
	TMT- A	p= 0.092*
	TMT –B	p= 0.0006*
PPE	p= 0.034*	
Seizure burden	Digit forward	P=0.057
	CATEGORICAL FLUENCY	p= 0.000*
	VERBAL 1 ERROR	p= 0.0266*
	VISUAL 1 HIT	p= 0.0079*
	WCST	
	No of correct Responses	p=0.0000
	Conceptual Level Responses	p=0.000
	Percentage of conceptual level responses	p=0.000
	Percentage of Perseverative errors	p=0.000
	No of categories completed	p=0.000
	Verbal 1 back	p=0.003
	Visual 1 back	
	Verbal 2 back	
	Visual 2 back	
	TMT B	P=0.00
Tower of London		
2MM	0.008	
3MT	0.027	
4MM	0.062	
IQ	0.02	

*Statistically significant.

visual 2 hits, 2&5 moves of Tower of London, IQ of the patients. Quality of life when compared with above parameters it is found that there is correlation only with increased number of AED s thereby suggesting that refractory patients using polytherapy are to have low quality of life. When tried to evaluate one single test to determine executive dysfunction in chronic temporal lobe epilepsy on multiple logistic regression, any one of the single test of extensive battery had no statistically significance for any test there by suggesting that there are multiple cognitive sub domains of temporal lobe epilepsy exists and monitoring one domain of executive function does not reveal the whole problem of its burden on temporal lobe epilepsy patients. We also found that though there is executive dysfunction in patients with chronic temporal lobe epilepsy, when compared with quality of life it is not get impaired which is statistically not significant.

Discussion

Executive functions include vital cognitive activities including decision making, planning, sustained attention, awareness and insight [10] which is necessary for activities of day to day life. So it may be expected that chronic MTLE patients experience executive function deficits which may impair day to day functioning of individuals that affects quality of life. In our study, an extensive neuropsychological test battery for executive function is used. Results indicated that MTLE patients showed statistically significant deficits in several executive function measures in all battery of tests and these results are similar to Black et al, Zamarian et al [11,12]. Severe executive dysfunction is noted in TLE indicate that the dysfunction of TLE extended beyond the anatomy to involve extra temporal abnormalities on the same side and opposite to the seizure onset which is similar to other studies by Hermann et al, Oyegbile et al, McDonald et al, Mueller et al [13-16]. The phenotype of executive dysfunction is noticed in a major proportion of TLE patients according to Dabbs et al, Hermann et al [17,18] In study by Dabbs et al [17] who tried to do cluster analysis found that the 25% of sample showed significant impairment in cognition, memory, executive function, psychomotor speed when compare to memory compromised group. Executive dysfunction that is best investigated by Wisconsin Card Sorting Task (WCST) [19,20] which will detect problems with set shifting. More perseverative errors are found without impairing other executive functions in hippocampal sclerosis (HS) than frontal lobe epilepsy according to corcoran and upton [21]. This evidence provides dissociation in various subgroups of executive functions. We also found after multivariate analysis, there is no single test that is common to detect executive dysfunction showing that individual domain which is unique to that patient is involved rather than one domain in all patients suggesting that various cognitive subtypes of TLE may exist. In our study we found that age of onset affects working memory, psychomotor speed & cognitive flexibility and planning only whereas according to Black et al, age of onset correlated significantly with various aspects of executive dysfunction [11]. There are not many studies which have shown the relation of frequency of seizures or seizure burden on executive dysfunction. In our study we found that seizure burden influences attention, fluency, set shifting, working memory, psychomotor speed & cognitive flexibility and planning. Polytherapy seems to affect working memory, fluency and planning which is similar to study by Kim et al [12,22]. In our study, disease duration affected working memory, psychomotor speed and cognitive flexibility and planning when

compared to study by Kim et al [22] that did not show correlation with frontal dysfunction but affected memory whereas Zamarian et al [12] showed correlation with frontal dysfunction. Martin et al did not report any correlation [23,24]. According to Struss et al set shifting is significantly impaired in left temporal lobe dysfunction if it occurs less than one year old [25]. When compared, set shifting involvement is less severe in Right temporal lobe involvement, but occurred independently of age of onset. But we could not find in our study this kind of difference in side of lesion. Side of lesion effects attention and planning and we did not found any difference between sides of lesion for specific domain as set shifting seen in Struss et al [25]. According to evidence from neuropsychological and neuro imaging, TLE can have compromised working memory and executive function, particular emphasis has been paid to set shifting as measured by the WCST. The cause executive skills weakness seems to be the propagation of seizure activity to executive skills dependant regions in the frontal lobes. With regard to working memory, the evidence more consistently supports direct role. There is role of temporal lobe in the encoding and maintenance of working memory had both hippocampal-dependent and independent processes. The cognitive phenotype and trajectory in TLE will likely vary depending on the underlying mechanism and this has clinical relevance important to establish further. Longitudinal neuropsychological and functional neuro imaging studies assessing frontal lobe functions and working memory pre- and post temporal lobe resections hold promise in elucidating the nature and mechanisms underlying frontal lobe dysfunction in TLE. Identification of mechanism of impairment will also help us to predict likely loss or gain of functions after surgical resection. We also found that though most of the patients had shown executive function it is not on same domain. We also propose to identify various cognitive subgroups of TLE to identify the treatment aspects accordingly.

Limitations of the Study

The role individual of anti-epileptic medication on frontal lobe function is not studied well.

Topiramate is found to negatively impact working memory [23,26]. Individual drugs should be explored by reassessing executive functions following drug discontinuation in seizure-free surgical patients. Our study is cross sectional observational study. A Longitudinal neuropsychological and functional MRI studies evaluating frontal lobe executive abilities and working memory in both pre- and post temporal lobe resections will help in the nature and mechanisms underlying frontal lobe dysfunction in TLE. Theory of mind appears vulnerable in TLE, which is not evaluated in the present study. A study on post operated patients is needed to know whether intervention affects the cognition.

Conclusion

Evidence for frontal lobe dysfunction noted in mesial temporal lobe epilepsies. Age of onset and duration of illness found to have effect on working memory, psychomotor speed & cognitive flexibility, planning. Side of lesion correlated well with Seizure frequency attention, fluency, set shifting, working memory, psychomotor speed & cognitive flexibility, planning, IQ, AEDS fluency, working memory, 3 planning , quality of life , intelligent quotient. Mesial temporal lobe

epilepsy has effects beyond temporal lobe suggesting the effect of epilepsy on networks.

References

- Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet Neurol.* 2004; 3: 663-672.
- Keller SS, Baker G, Downes JJ, Roberts N. Quantitative MRI of the prefrontal cortex and executive function in patients with temporal lobe epilepsy. *Epilepsy Behav.* 2009; 15: 186-195.
- Ragland JD, Yoon J, Minzenberg MJ, Carter CS. Neuroimaging of cognitive disability in schizophrenia: search for a Pathophysiological mechanism. *Int Rev Psychiatry.* 2007; 19: 417-427.
- Hanna-Pladdy B. Dysexecutive syndromes in neurologic disease. *J Neurol Phys Ther.* 2007; 31: 119-127.
- Linden DE. The working memory networks of the human brain. *Neuroscientist.* 2007; 13: 257-267.
- Gilbert SJ, Burgess PW. Executive function. *Curr.Biol.* 2008; 18: 110-114.
- Ehlhardt LA, Sohlberg MM, Kennedy M, Coelho C, Ylvisaker M, Turkstra L, et al. Evidence-based practice guidelines for instructing individuals with neurogenic memory impairments: what have we learned in the past 20 years?. *Neuropsychol. Rehabil.* 2008; 18: 300-342.
- Devinsky O. The myth of the silent cortex and the morbidity of epileptogenic tissue: implications for temporal lobectomy. *Epilepsy Behav.* 2005; 7: 383-389.
- Abrahams S, Morris RG, Polkey CE, Jarosz JM, Cox TC, Graves M, et al. Hippocampal involvement in Spatial and working memory, a structural MRI analysis of patients With unilateral mesial temporal lobe sclerosis. *Brain Cogn.* 1999; 41: 39-65.
- J Stretton, PJ Thompson. Frontal lobe function in temporal lobe epilepsy. *Epilepsy Research.* 2012; 98: 1-13.
- Black LC, Schefft BK, Howe SR, Szaflarski JP, Yeh S, Privitera MD. The effect of seizures on working Memory and executive functioning performance. *Epilepsy Behav.* 2010; 17: 412-419.
- Zamarianet al. Cognitive Effects of Low-dose Topiramate Compared with Oxcarbazepine in Epilepsy Patients. *J Clinical Neurol.* 2006; 2: 126-133.
- Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Arch Neurol.* 1997; 54: 369-376.
- Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R., Seidenberg M, Hermann BP. The nature and course of Neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology.* 2004; 62: 1736-1742.
- McDonald CR, Delis DC, Norman MA, Tecoma ES, Iragui Madozi VI. Is impairment in set-shifting specific to frontal-lobe dysfunction? Evidence from patients with frontal lobe or temporal-lobe epilepsy. *J Int Neuropsychol Soc.* 2005; 11: 477-481. Mueller SG, Laxer KD, Barakos J, Cheong I, Finlay D, Garcia P, et al. Involvement of the thalamocortical network in TLE with and without mesiotemporal sclerosis. *Epilepsia.* 2009; 51: 1436-1445.
- Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. *Epilepsy Behav.* 2009; 15: 445-451.
- Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy *J Int Neuropsychol Soc.* 2007; 13: 12-20.
- Berg EA. A simple objective technique for measuring flexibility in thinking. *J Gen Psychol.* 1948; 39, 15-22.
- Heaton RK. Wisconsin Card Sorting Test Manual. Psychological Assessment Resources, Inc, Odessa, FL. 1981.
- Corcoran R, Upton D. A role for the hippocampus in card sorting?. *Cortex.* 1993; 29: 293-304.
- Kim SY, Lee HW, Jung DK, Suh CK, Park SP. Cognitive effects of low-dose topiramate compared with oxcarbazepine in epilepsy patients. *J Clin Neurol.* 2006; 2: 126-133.
- Martin R, Dowler R, Gilliam F, Faught E, Morawetz R, Kuzniecky R. Cognitive consequences of coexisting temporal lobe developmental malformations and hippocampal sclerosis. *Neurology.* 1999; 53: 709-715.
- Martin RC, Sawrie SM, Edwards R, Roth DL, Faught E, Kuzniecky RI, et al. Investigation of executive function change following anterior temporal lobectomy, selective normalization of verbal fluency. *Neuropsychology.* 2000; 14: 501-508.
- Strauss E, Hunter M, Wada J. Wisconsin card sorting performance, effects of age of onset of damage and laterality of dysfunction. *J Clin Exp Neuropsychol.* 1993; 15: 896-902.
- Smith ME, Gevins A, McEvoy LK, Meador KJ, Ray PG, Gilliam F. Distinct cognitive neurophysiologic profiles for lamotrigine and topiramate. *Epilepsia.* 2006; 47: 695-703.