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Original Research Article

Neourodynamics in patient with Alzheimer's disease during working memory task

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Abstract: The aim of the present study was to evaluate the behaviour of memory-related electroencephalographic measures in patients with Amnesic Alzheimer's disease. Electroencephalography (EEG) was recorded during working memory test (LB-memory test) in age-sex matched 30 normal elderly subjects and 20 amnesic Alzheimer's disease patients (55-75 years). The EEG bands so evaluated were delta (0.2-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.1- 12.9 Hz), beta (13.0 -30.0 Hz) and gamma (30.1-80 Hz). A significant decrease Mini Mental State Examination (MMSE) score was observed in patients when compared to controls (p=0.000). Amnesic Alzheimer's patients showed significant decreased working memory scores in List A (p=0.038), List B (p=0.003) and List C (p=0.000), decreased absolute power in delta, theta, alpha, beta and gamma in fronto-central and temporal regions and significant decreased coherence in frontal (F3-F4) and temporal (T3-T4) lobes in alpha-1(8-9.9 Hz), alpha-2 (10-12.9 Hz) and beta (13-30 Hz) bands (p=0.000) during working memory task as compared to healthy, age and sex matched control subjects. These results suggest that absolute power and coherence during working memory task can discriminate Amnesic Alzheimer's patients from normal elderly subjects.
Keywords: Amnesic Alzheimer's disease, Electroencephalography (EEG), Mini Mental State Examination (MMSE), working memory task, Absolute power, Coherence

INTRODUCTION

The German Physician, Alois Alzheimer (in 1906) was the first to profile and define the clinical entity of Alzheimer's disease (AD) as a form of dementia way. Clinically diagnosed Alzheimer's disease, alone or in combination with other illness, accounts for up to 90% of reported dementia cases in the west [1]. Incidence rate of Alzheimer' disease was 9.19 (9.03-9.35) per 1000 person-years, reported from southern India [2]. The pathophysiology of Alzheimer's disease has been hypothesized and documented to be dysfunction of synaptic mechanisms with loss of functional neuronal pools. The features of Alzheimer disease are progressive deficits in memory and other aspects of cognition. Due to the deficits, patients with Alzheimer disease are unable to perform their daily course, leading to total dependence on their caregivers [3]. The deficits in memory result from synaptic dysfunction and neuronal loss. Dysfunctions primarily in the hippocampus, limbic cortex, and polymodal association cortex have been implicated in the genesis and evolution of Alzheimer's disease [3].

Memory dysfunction is the first symptom which is recognized in Alzheimer's disease. It is detectable by neuropsychological tests in preclinical phases of the disease [4]. The typical memory impairment at onset involves difficulties with learning

new information with relative preservation of remote factual information. Alzheimer's disease related memory changes usually include short-term memory loss. Recent memories are impaired because new information cannot be adequately acquired, represented and stored for later recall. Persons with memory loss initially present with the inability to remember recent events. In later stages, memory dysfunction extend to complete failure of recall for previously well remembered information, such as the names of a patient's own spouse and children [3].

Neuritic plaques and neurofibrillary tangles are the most important and characteristic pathognomic features in patients of Alzheimer's disease. Oligomers of amyloid beta (Aβ) cause synaptic loss by inducing metabolic and morphologic changes in pyramidal neurons of the hippocampus and neo-cortex that lead to cognitive decline in symptom complex of Alzheimer's disease [5]. Aβ oligomers have been postulated to induce synaptic dysfunction with altered glutamate transmission, impairment of the long term potentiation (LTP) and facilitation prolonged long term depression (LTD), with subsequent spine shrinkage and activation of enzymatic pathways leading to apoptosis and cell death [6]. Acetylcholine is a neurotransmitter that has been implicated in cognitive neurophysiology and severity of the diseases has been observed to be correlated with the loss of cerebral cortical markers for acetylcholine metabolism [7]. Short-term memory, known as "primary" or "active" memory, is the part of memory which stores a limited amount of information for a limited amount of time (roughly 15-30 seconds). Working memory is the ability of storing and manipulating information for only a short period of time, if not rehearsed will be lost in 20 second or so [8]. Information can be kept in the working memory by repetition as working memory gets forgotten easily in presence of any kind of disturbance. Working memory comprises both executive attention and memory process [8].

Prefrontal cortex appears to play a fundamental role in short-term and working memory. It serves as a temporary store for short-term memory, where information is made available and provided whenever it is needed for current reasoning processes elsewhere in the brain [9]. The central executive part of the prefrontal cortex controls two neural loops, one for visual data, which activates areas near the visual cortex of the brain and acts as a visual scratch pad, and other for language, the phonological loop, which uses Broca's area as a kind of inner voice that repeats word sounds to keep them in mind. These two scratch pads temporarily hold data until it is erased by the next information. Lesion in the prefrontal cortex causes short-term memory impairment. In situations of short-term memory loss generation and transmission of meaningful nerve impulse ceases to exist in the dedicated neuronal network and/or pool. In general, unless an impulse is reactivated, it stops flowing through a network after just a few seconds [9].

Promising markers of functional neural connectivity derive from the measurement of the functional coupling of resting state eyes closed EEG rhythms between pairs of electrodes. Linear components of such coupling, functional co-ordination, and mutual information exchange can be evaluated by the analysis of spectral coherence [10, 11]. Spectral coherence is a normalized value that quantifies the temporal synchronization of two EEG time series between pairs of electrodes in the frequency domain and can be derived by Fast Fourier Transform (FFT) [12, 13].In this context the present study was undertaken to explore neural dynamics as patterned through EEG rhythm during working memory task and to appreciate an insight into the functioning of human mind in relation to cognitive decline.

MATERIALS AND METHODS

The study was conducted in the Department of Physiology in association with the Department of Neurology, S.M.S. Medical College, Jaipur and the Department of Neurosciences (Cognitive Function Section), Santokaba Durlabhji Memorial Hospital (SDMH), Jaipur. The study design was a hospital based observational case - control study. All experimental protocols had been approved by the Institutional Ethics Committee. Thirty healthy controls and twenty Amnesic Alzheimer's disease patients were enrolled in the present study. The Alzheimer's patients were recruited from the O.P.D. of Neurology, S.M.S. Medical College, Jaipur and the Department of Neurosciences (Cognitive Function Section), SDMH, Jaipur. All patients underwent history taking, physical and neurological examination, psychometric testing and neuroimaging procedures (magnetic resonance imaging, MRI with temporal lobe protocol of the brain) and laboratory testing to rule out other causes of cognitive impairment. The control group for study was composed of age and sex matched healthy subjects from the Institute.

The inclusion criteria adopted for the present study were: patients between 55 – 75 yrs., complaint by

the patient, or report by a relative or the general practitioner of memory or other cognitive disturbances; patients rated and categorized with the standardized diagnostic and severity instrument of Mini Mental State Examination (MMSE) [14]. Patient with fronto-temporal dementia, vascular dementia based on clinical and radiological grounds, extrapyramidal syndrome, psychiatric diseases, epilepsy, drug addiction, alcohol dependence, current or previous uncontrolled systemic diseases, traumatic brain injuries were excluded for the study.

EEG recordings

The EEG activity was recorded, continuously by using electrodes set in an elastic cap (Electro - Cap International,) and positioned according to the 10–20 international system (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, Oz, O1, O2). Impedance was kept below 5 Ω and electrical activities, amplified with a band-pass filter of 0.5 - 30.0 Hz, were digitized at sampling rate 256 Hz. Recording of EEG was taken in a sound attenuated, dimly lit room. The patients were instructed to stay sit with closed eyes and relaxed and were awake during the procedure of basal and specialized manoeuvres EEG - test run. The EEG bands we use so evaluated were delta (0.2-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.1- 12.9 Hz), beta (13.0 -30.0 Hz) and gamma (30.1-80 Hz). QEEG was done for all the patients and controls using BESS (brain electro scan software) of the Axxonet System (India). Artefact free epochs of 2 seconds each were chosen because after every of 2-3 seconds the changes both inclusive and exclusive in the amplitude were taking place more than 10% and their spectral content evaluated by means of Fast Fourier Transform analysis [15].

Working Memory Task

After recording in the rest condition the working memory task was performed. Patients were instructed to hear word list carefully and were asked to repeat the word list during which time – course the EEG was recorded with eyes closed. Memory tasks (named as: List A, List B, and List C) involve the sequential acquisition and immediate recall of 3 word lists. List A consists of 18 semantically unrelated items; whereas Lists B and C present 18 semantically-related items, equally distributed across 3 different mutually-exclusive taxonomic categories, 6 items for each category. The automatic scoring system provides the profile of results for each subject.The score of working memory performance was computed as the total number of correctly remembered words. It was ensured that at the time of EEG recording, the subject was not on any medication that influenced the EEG rhythm [16].

Statistical analysis

The Microsoft excel 2007 was used for statistically analysis of data. The unpaired t-test was used for the mean comparison of all parameters between patients with Alzheimer's disease and control subjects. With intention to avoid type 2 errors, we considered two – sided p values < 0.05 to be significant.

RESULTS

Table-1: Demographic and clinical data of the Alzheimer's disease and control population

Demographic and clinical Variables		Patient (N=20)	Control (N=30)	p value
Gender	Male	11	21	0.281
	Female	9	9	0.281
Age	Mean	69.10	66.63	0.124
	SD	6.146	3.986	
MMSE Score	Mean	12.75	28.23	0.000
	SD	3.537	1.194	

Table-2: Working Memory Task Score of the Alzheimer's disease and control population

Working Memory Task Score					
List	Control(30)		Patient(20)		p value
	Mean	SD	Mean	SD	
List A	34.67	17.122	24.93	13.701	0.039
List B	39.78	15.995	25.84	15.542	0.004
List C	45.04	17.076	19.38	12.299	0.000

Table-3: Absolute power of EEG band of delta, theta, alpha, beta, gamma in fronto-central region during working memory task

EEG Band	Control	Patient	p value
Delta	37.64(17.68)	27.17(13.69)	0.000
Theta	15.62(7.81)	10.58(4.65)	0.000
Alpha	9.99(5.07)	5.13(2.96)	0.000
Beta	13.80(6.40)	7.71(4.91)	0.000
Gamma	11.74(5.17)	5.91(5.31)	0.000

Table-4: Absolute power of EEG band of delta, theta, alpha, beta and gamma in temporal region during working memory task

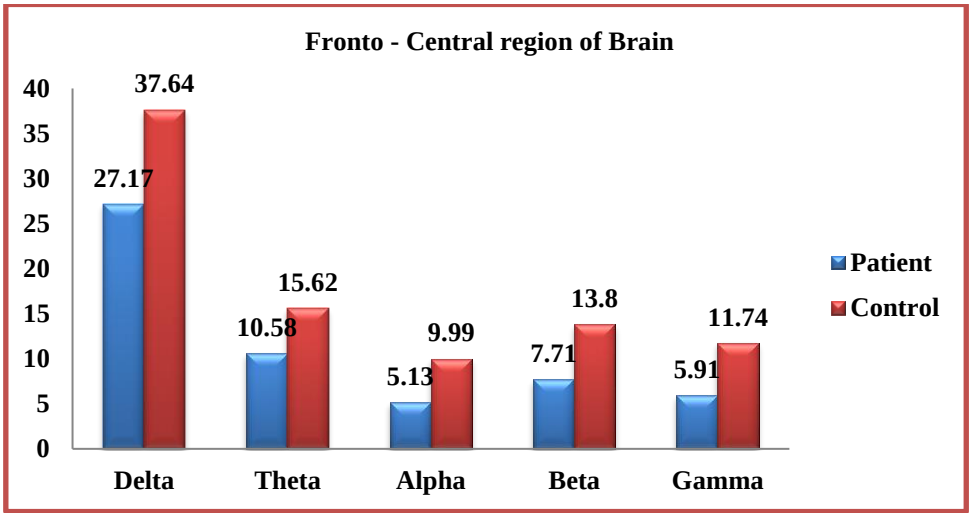
EEG Band	Control	Patient	p value
Delta	33.14(16.09)	26.90(10.90)	0.176
Theta	15.49(7.77)	10.48(4.07)	0.015
Alpha	11.08(5.46)	5.23(3.03)	0.000
Beta	13.61(6.31)	6.69(4.61)	0.000
Gamma	11.07(5.16)	5.10(5.07)	0.000

Table-5: Spectral coherence of EEG band of delta, theta, alpha-1, alpha-2, beta in F3-F4 electrodes

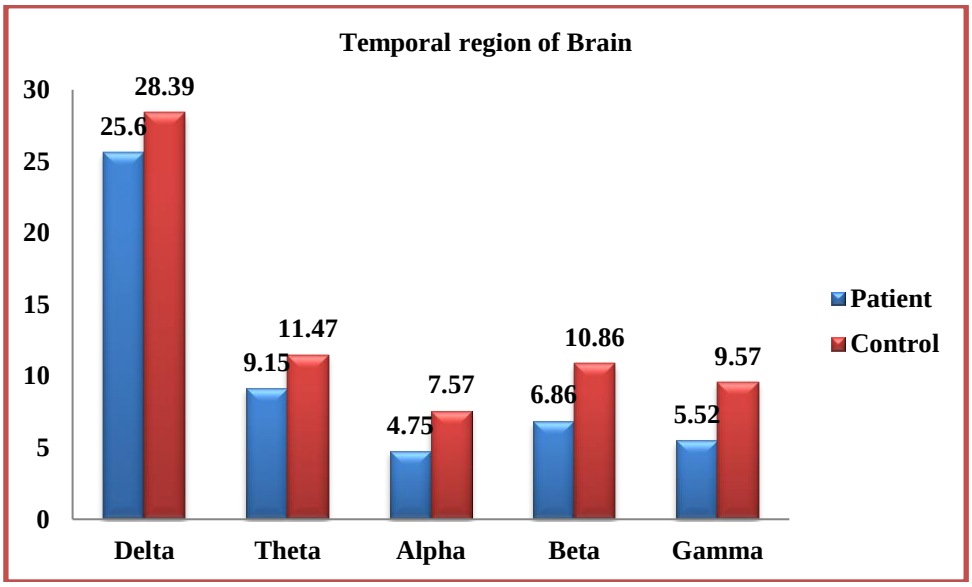
EEG Band	Control	Patient	p value
Delta	0.476(0.365)	0.519(0.283)	0.663
Theta	0.513(0.298)	0.471(0.228)	0.599
Alpha-1	0.521(0.290)	0.305(0.239)	0.008
Alpha-2	0.495(0.297)	0.245(0.219)	0.002
Beta	0.478(0.252)	0.295(0.175)	0.007

Table-6: Spectral coherence of EEG band of delta, theta, alpha-1, alpha-2, beta in T3-T4 electrodes

	Control	Patient	p value
Delta	0.586(0.225)	0.481(0.192)	0.096
Theta	0.601(0.241)	0.367(0.189)	0.001
Alpha-1	0.428(0.311)	0.125(0.141)	0.000
Alpha-2	0.378(0.318)	0.138(0.158)	0.003
Beta	0.360(0.295)	0.146(0.111)	0.003



Graph-1: Absolute Power of EEG band of delta, theta, alpha, beta and gamma during Memory task Session



Graph-2: Absolute Power of EEG band of delta, theta, alpha, beta and gamma during Memory task Session

In the present study lower working memory scores was registered in List A (p=0.038), List B (p=0.003) and List C (p=0.000) in AD patients as compared to healthy, age and sex matched population (Table 2). During working memory task fronto- central delta, theta, alpha, beta and gamma (p=0.000) absolute power decreased when compared to healthy, age and sex matched control subjects (Table 3, graph 1). During working memory task temporal delta (p=0.176), theta (p=0.015), alpha, beta and gamma (p=0.000) bands absolute power decreased when compared to healthy, age and sex matched control subjects (Table 4, graph 2).

In the present study decreased coherence was found in patients with Amnesic Alzheimer's disease in theta (p=0.599), alpha-1 (p=0.008), alpha-2 (p=0.002) and beta (p=0.007) band at F3-F4 electrodes (Table 5) when compared to healthy, age and sex matched control subjects. Interestingly, at delta band (p=0.663) increased coherence was reported at F3-F4 electrodes (Table 5) in patients with Amnesic Alzheimer's disease when compared to healthy, age and sex matched control subjects. Reduced coherence was observed at T3-T4 electrodes at delta (p=0.096), theta (p=0.001), alpha-1 (p=0.000), alpha-2 (0.003) and beta (p=0.003) in patients with Amnesic Alzheimer's disease when compared to healthy, age and sex matched control subjects.

DISCUSSION

Multiple brain areas, including the lateral prefrontal cortex, mediotemporal areas and posterior association cortex are functionally involved in working memory [17]. Working memory functions have been associated with an increase of power in the theta band [18]. High spectral coherence and linear correlation are shown by the functionally coordinated two cortical areas. Reduced linear functional coupling and information transfer among cortical areas are reflected as decrease of coherence whereas an increase of the coherence values is interpreted as an enhancement of the linear functional connections and information transfer which reflects the interaction of different cortical structures for a given task. Spectral coherence may reflect the integrity of cortical neural pathways [19]. Using the measure as the linear and non-linear statistical dependencies between two time series (cross-mutual information), indeed loss of functional connectivity has been demonstrated in patients with AD, in particular over the frontal and anterior-temporal regions [20].

Increased alpha power over temporal cortex in healthy controls and reduced alpha coherence in temporal cortex was reported in AD patients [21]. These findings supports the present study in which increased alpha power was documented in healthy controls in temporal region and reduced coherence in temporal cortex was reported in AD patients. Reduced coherence between temporal lobes is discussed in light of a neurological

model of AD that hypothesized reduced electrocortical efficiency and a breakdown of neural network communication to temporal lobes, possibly resulting from temporal lobe atrophy [21]. Increased coherence in alpha-1 band was observed in the control group following the cognitive task [22]. In the present study same finding was observed during working memory task in the both frontal (F3-F4 electrodes) and temporal lobe (T3-T4 electrodes). EEG parameters calculated from epochs following the completion of a cognitive task clearly differentiates patients with AD from normal controls [22]. Higher mean value of beta band was reported in AD compared to controls during the Paced Auditory Serial Addition Test [23].

Significant decreased synchronization likelihood was observed in the alpha -2 (upper alpha) and beta bands in AD compared to control subjects during a working memory task [24]. It is conceivable that slowing of background activity in a certain frequency band is accompanied by a decrease of synchronization likelihood in that frequency band, indicating the loss of functional interactions. It is known that in particular long distance association fibres degenerate in AD, predated by a loss of cholinergic innervations [25, 26].

CONCLUSION

The present study concluded that decreased power and coherence in frontal and temporal lobe during a working memory task can differentiate the patients with Alzheimer's disease from the normal healthy control group. Future investigations are needed to validate the clinical usefulness of these findings in early differential diagnosis, disease staging, and therapy monitoring.

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