ASSESSMENT OF COGNITIVE FUNCTION IN PATIENTS WITH DIABETES MELLITUS TYPE 2

BY

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DISSERTATION SUBMITTED TO THE
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Under the guidance of

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DEPARTMENT OF PHYSIOLOGY
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A WORD OF GRATITUDE

To my respected teacher and guide:

Dr. Vinutha Shankar M.S. ***M.D***
Professor
Department of Physiology
Sri Devaraj Urs Medical College,
Kolar.

Though words falter to acknowledge all my debt, it is with a deep sense of gratitude that I express my thanks to my reverend, renowned Teacher, Guide and Professor Dr. Vinutha Shankar M.S, Department of Physiology whose dynamic personality, mature and friendly attitude, relentless help, proficient ideas, constant supervision, direction, discussion and inspiration has guided me throughout my post-graduate career. I am thankful for her act of kindness in taking immense interest in my dissertation work.

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In the end, I thank The Almighty for the blessing for the fulfillment of this work.

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LIST OF ABBREVIATIONS

T2DM	-	Type 2 diabetics
ERP	-	Event related potentials
MMSE	-	Mini mental state examination
ms	-	milliseconds
P300	-	Positive P300 wave
P3	-	Positive P300 wave
EEG	-	Electroencephalography
MEG	-	Magnetic encephalography
PET	-	positron emission tomography
PTA	-	Pure Tone Audiometer
NIHL	-	Noise Induced Hearing Loss
AC & BC	-	Air Conduction & Bone Conduction
KHz	-	Kilo Hertz
Dba	-	Decibel, SPL measured with “A” weighting network

ABSTRACT

Background and objectives:

There is increasing interest in the impact of diabetes mellitus on cognitive functioning. Several studies found evidence of decreased cognitive performance in type 2 diabetics (T2DM). Less attention has been given to the effect of diabetes on cognitive function. Since the P300 component of event-related potentials (ERPs) provides valuable information concerning cognition, we studied this component of ERPs in T2DM.The aims of this study were to evaluate the cognitive status of outpatients with type 2 diabetes and to evaluate factors associated with impaired cognitive functions.

Materials & Methods:

30 Type 2 Diabetes Mellitus patients and 30 age and sex-matched controls were selected considering inclusion & exclusion criteria. These two groups were asked to fill questionnaire Folstein mini-mental state examination (MMSE) for assessing cognitive function and those showing scores more than 25 (maximum score= 30) were enrolled for the study. Pure tone audiometry (PTA) was done to screen for hearing loss and after hearing loss was ruled out, P300 recording was done on them using RMS EMG EP MARK II machine. The resulting data was statistically analysed.

Results:

Compared with controls, diabetics had significantly longer P300 latencies ($p=0.001^{**}$).In addition, P300 latencies showed significant positive correlation ($r=0.390^{*}$; $p=0.033$) with disease duration. Significant difference was found in P300

latency between diabetic hypertensives (p=0.003) and diabetic nonhypertensives and also among diabetics with dyslipidemia(p=0.047) and diabetics without dyslipidemia. Significant difference was also observed in P300 latency between diabetic smokers (p=0.001) and diabetic non-smokers.

Conclusions:

P300 ERPs revealed cognitive dysfunction which was not detected by neuro-psychometric test (MMSE). Our findings suggest that surface-recorded ERPs may be useful for detecting and monitoring the changes in brain function associated with diabetes mellitus. Patients with type 2 diabetes should be regularly evaluated for their cognitive function, because duration of disease could be associated with decline in cognition. Co-existence of hypertension, dyslipidemia and smoking with T2DM further increases the risk of cognitive impairment. We conclude that ERP P300 can be done to detect early stages of dementia.

Key words: ERP, Cognitive impairment, T2DM, MMSE, Dementia

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INTRODUCTION

INTRODUCTION

DIABETES MELLITUS is a complex metabolic disease that can have devastating effects on multiple organs in the body[1,2] The deleterious effects of diabetes mellitus on the retinal, renal, cardiovascular, and peripheral nervous systems are widely acknowledged. A less addressed and not as well recognized complication of diabetes is cognitive dysfunction. Both type 1 and type 2 diabetes mellitus have been associated with reduced performance on numerous domains of cognitive function. The exact pathophysiology of cognitive dysfunction in diabetes is not completely understood, but it is likely that hyperglycemia, vascular disease, hypoglycemia and insulin resistance play significant roles. Modalities to study the effect of diabetes on the brain have evolved over the years including neurocognitive testing, evoked response potentials, and magnetic resonance imaging.[1,2]

As DM increasingly becomes a disease of older adults, some of its underappreciated cognitive manifestations must be addressed. Cognitive dysfunction which imposes a direct impact on quality of life, loss of independence and demands on caregivers may ultimately be as great a concern to older adults with diabetes as the more traditionally recognized vascular complications.[3]

Besides diabetes, these patients usually have other comorbidities such as hypertension, and dyslipidemia. Today there is strong evidence suggesting association of cognition with these comorbidies.[4,5]

Among the neuropsychological tests, the Mini-mental state examination (MMSE) is one of the most widely used screening tests.[6,7] This test which differentiates patients with non-specified organic brain syndrome and depression from normal individuals is also useful to estimate the severity of cognitive impairment and in documenting serially cognitive changes. The performance in the MMSE can be

influenced by age and education level.[8]

Most patients with diabetes have subtle cognitive deficits that may easily go undetected using gross screening instruments such as MMSE. Numerous studies have shown that MMSE has poor sensitivity and specificity as well as a low test retest reliability.[7]

Event-related potentials (ERPs) provide a non invasive method of studying brain neural activity with a temporal resolution reflecting the speed of cognitive processes. P300 latency is considered an electrophysiological index of the relative timing of the stimulus evaluation process and cognitive impairment in recent years.[9,10] P300 has been used extensively in investigations of psychiatric and neurological disorders involving cognitive abilities. Alterations of its latency have been described, appearing to reflect deficits in cognitive processing.[11,12,13]

An electrophysiological test, P300 cognitive potential was included in the study to detect cognitive dysfunction, which was not detected by neuro-psychometric test (MMSE).

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

1. To assess P300 latency in diabetics to test cognition and compare it with that of age and sex matched controls.
2. To correlate P300 latency with duration of diabetes.
3. To study the association of P300 latency with the coexisting conditions of diabetes like hypertension, dyslipidemia and smoking in diabetics.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

A. HISTORY:

1. In 1922, Miles and Root were the first to describe a possible relation between diabetes and cognitive dysfunction. They observed worse performance of patients with diabetes on measures of memory, arithmetic and psychomotor speed compared to non-diabetic persons.[14]

2. 1929- Hans Berger reported a remarkable and controversial set of experiments in which he showed that one could measure the electrical activity of the human brain by placing an electrode on the scalp, amplifying the signal and plotting the changes in voltage over time. This electrical activity is called the electroencephalogram, or EEG.[15]

3. 1934- Adrian & Matthews also observed human EEG activity, and Jasper and Carmichael (1935) and Gibbs, Davis and Lennox (1935) confirmed the details of Berger's observations. These findings led to the acceptance of the EEG as a real phenomenon.[15]

4. 1935–1936 -The first unambiguous sensory ERP recordings from awake humans were performed by Pauline and Hallowell Davis and published a few years later.[15]

5. 1956 -The official beginning of cognitive science is usually placed as the Dartmouth symposium on information theory.

   In cognitive psychology, George Miller published his seminal paper on short-term memory capacity 7±2 and Leon Festinger published his work on cognitive dissonance.[16]

6. 1956- Artificial intelligence was born as a discipline.[16]

7. 1962-The first published computer-averaged ERP waveform were apparently

published by Galambos and Sheatz. [15]

8. 1964- The modern era of ERP research began, when Grey Walter and his colleagues reported the first cognitive ERP component, which they called the contingent negative variation or CNV.[15]
9. 1965-The P3 component was discovered by Sutton, Braren, Zubin and John. Over the ensuing fifteen years, a great deal of research focused on identifying various cognitive ERP components and developing methods for recording and analyzing ERPs in cognitive experiments.[15]

ERPs were originally called evoked potentials (EPs) because they were electrical potentials that were evoked by stimuli (as opposed to the spontaneous EEG rhythms). Since cerebral processes may be related to voluntary movement and to relatively stimulus-independent psychological processes, the term ‘‘evoked potentials’’ is no longer sufficiently general to apply to all EEG phenomena related to sensory motor processes. Moreover, sufficiently prominent or distinctive psychological events may serve as time references for averaging, in addition to stimuli and motor responses.

10. 1969-The earliest published use of the term ‘‘event-related potential’’ by Herb Vaughan was found.[15]

The term ‘‘event related potentials’’ (ERP) is proposed to designate the general class of potentials that display stable time relationships to a definable reference event. Advances in key interfacing disciplines, especially computer science, psychology, neuroscience and linguistics, enabled the development of cognitive science as a discipline of its own for studying the mind. In the last fifty years, cognitive science and its interfacing disciplines have developed at a tremendous pace resulting in an a significant expansion of research on the brain, intelligent machines and the mind. [16]

B.COGNITION:

Cognitive science can be roughly defined as the study of the mind or mental processes. Cognitive science has also been defined as the study of the nature of intelligence. According to the Stanford Encyclopaedia of Philosophy, cognitive science 'is the interdisciplinary study of mind and intelligence, embracing philosophy, psychology, artificial intelligence, neuroscience, linguistics and anthropology'. In contrast, Mandler in 1986 has said that after twenty-five years, there is no single definition of cognitive science. Cognitive science as a discipline is relatively new in India. [16]

Cognitive means "knowing" and cognitive processes refer to the ways in which knowledge is gained, used and retained. Therefore, cognitive psychologists have studied cognitive functions such as attention, memory, perception, think, language, problem solving and Artificial intelligence etc.[17]

INFORMATION-PROCESSING APPROACH:

Thagard in 2005 said that the predominant approach in the study of mind is the computational theory of mind. It aims to understand the mind in terms of processes that operate on representations. [16]

Cognitive psychology sees the individual as a processor of information, in much the same way that a computer takes in information and follows a program to produce an output. Cognitive psychology compares the human mind to a computer**.**

The Information Processing System

Information processing models consist of a series of stages, or boxes, which represent stages of processing. Arrows indicate the flow of information from one stage to the next.

Input processes are concerned with the analysis of the stimuli.

Storage processes cover everything that happens to stimuli internally in the brain and can include coding and manipulation of the stimuli.

Output processes are responsible for preparing an appropriate response to a stimulus.[17]

COGNITIVE PROCESSES:

Cognitive psychology states that important cognitive processes occur between a stimulus and response. [17] Research on cognitive processes, including perception, attention, language, and decision making, has been flourishing for the past fifty areas. Prominent successes include the development of signal detection theory, the notion of multiple memory systems, models for different domains like reading, a better understanding of language comprehension and production, path-breaking research on decision making; and understanding of the different attentional processes.In the Indian context, research on cognitive processes has increased in the past few years.[16]

THE PROMISE OF COGNITIVE NEUROSCIENCE:

Cognitive neuroscience has employed multiple techniques to study cognition, including single-cell electrophysiology, lesion studies, brain stimulation, electroencephalography(EEG) and event-related potentials (ERP), magnetic encephalography (MEG),neuroimaging using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation. Single-cell electrophysiology has enabled us to understand the computational mechanisms underlying cognition by linking behaviour with electrophysiological responses.

The EEG methodology consists of non-invasive recordings of brain electrical activity that includes the measurement of ERP waveforms evoked in response to external stimuli. The ERP waveforms are computed by averaging time-locked EEG signals and different components are identified in the ERP waveforms that may correspond to specific cognitive processes. Spectral analysis of EEG provides information about different rhythms that play a critical role in cognition. The analysis of EEG signals also can provide a measure of synchronized activity of different brain regions under different conditions. Spatial localization of cognitive processes has been aided by the development of neuroimaging techniques. The fMRI methodology measures the hemodynamic response associated with neural activity in the brain.

Bechtel and Richardson have argued that the main purpose of neuroimaging is to provide a way to functionally decompose cognitive processes rather than just localization of functions. [16]

C. NEURAL BASIS OF COGNITIVE FUNCTION:

Cognitive Functions Are Localized Within the Cerebral Cortex

The brain operations responsible for our cognitive abilities occur primarily in the *cerebral cortex* —the furrowed gray matter covering the cerebral hemispheres. In each of the brain's two hemispheres the overlying cortex is divided into four anatomically distinct lobes: *frontal, parietal, temporal,* and *occipital* (see Figure 1), originally named for the skull bones that encase them. These lobes have specialized functions. The frontal lobe is largely concerned with planning future action and with the control of movement; the parietal lobe with somatic sensation, with forming a body image, and with relating one's body image with extrapersonal space; the occipital lobe with vision; the temporal lobe with hearing; and through its deep structures—the hippocampus and the amygdaloid nuclei—with aspects of learning, memory, and emotion. Each lobe has several characteristic deep infoldings (a favored evolutionary strategy for packing in more cells in a limited space). The crests of these convolutions are called *gyri,* while the intervening grooves are called *sulci* or *fissures*. The more prominent gyri and sulci are quite similar in everyone and have specific names. For example, the *central sulcus* separates the *precentral gyrus,* which is concerned with motor function, from the *postcentral gyrus,* which is concerned with sensory function

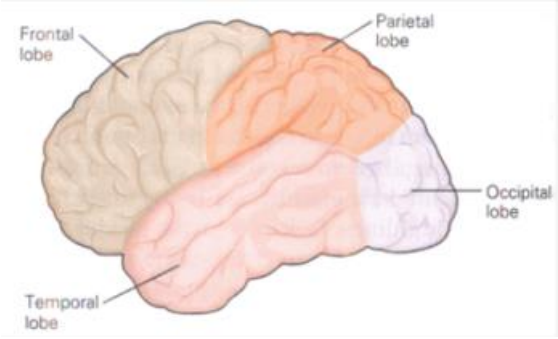

Fig.1:The four lobes of cerebral cortex[18]

The organization of the cerebral cortex is characterized by two important features.

First, each hemisphere is concerned primarily with sensory and motor processes on the contralateral (opposite) side of the body.

Second, although the hemispheres are similar in appearance, they are not completely symmetrical in structure nor equivalent in function.[18]

PREFRONTAL CORTEX:

Prefrontal cortex (PFC) is defined as that part of frontal cortex that lies anterior and medial to the motor and premotor cortex. In primates, the territory is vast and is far less well understood both anatomically and physiologically than the sensory systems in the more posterior regions of the brain. Experimentally, prefrontal cortex has been much more difficult to explore than sensory systems, largely because its neurons are many synapses distant both from the receptor surfaces and from the motoneuron-muscle interface. Given PFC input from brainstem and subcortical structures, it is not surprising that the specific neuronal response patterns, even when found, may be difficult to interpret.[19]

HIPPOCAMPUS AND AMYGDALA:

Limbic structures, emotions and drives

The limbic structures are a highly interconnected set of subcortical regions that include the hippocampus, amygdala, basal forebrain and hypothalamus. The only cortical structure included is the cingulate cortex – that part of the medial cortex that forms a band bordering the cerebral commissures. Activity in all these structures is modulated by the main four neurotransmitter systems originating in distinct brainstem nuclei and identified in terms of their specific transmitter: dopamine, serotonin,

noradrenalin and acetylcholine. Changes in these systems can have powerful effects on cognition, consciousness, anxiety levels, aggressiveness, sexual drive, moods and on the emotions.[19]

THE AMYGDALA

The amygdala is a multi-component structure, highly connected to prefrontal cortex, and to other limbic structures, including the hippocampus and the basal forebrain. One specific component (the lateral nucleus) has been identified as crucial for aversive-conditioning, for negative feelings such as fear, and for recognizing a situation as fearful and a face as showing fear. Other regions of the amygdala form part of the complex reward circuitry involving the positive emotions. [19]

Adolphs et al. (1998) report that the amygdala is critical for aiding retrieval of socially relevant knowledge about facial appearance. [19]

CHOLINERGIC INNERVATION IS ASSOCIATED WITH COGNITIVE FUNCTION:

The primacy of the hippocampus and its connections with the base of the forebrain for memory formation implicates acetylcholine as a major transmitter in cognitive function and learning and memory. The basal forebrain region contains prominent populations of cholinergic neurons (**basal forebrain nuclei)** that project to the hippocampus and to all regions of the cerebral cortex. Another major cholinergic projection derives from a region of the brainstem reticular formation known as the **pedunculopontine nucleus**, which projects to the thalamus, spinal cord and other regions of the brainstem. Roughly 90% of brainstem inputs to all nuclei of the thalamus are cholinergic.

Cortical cholinergic connections are thought to control selective attention, a

function congruent with the cholinergic brainstem projections through the ascending reticular activating system. Loss of cholinergic function is associated with **dementia**, an impairment of memory, abstract thinking and judgment. Other cholinergic neurons include motor neurons and autonomic preganglionic neurons, as well as a major interneuronal pool in the striatum.[20]

ASSOCIATION AREAS:

Indeed, many scientists thought that cognitive functions, because of their complexity, required the operation of the brain as a whole. Only in the last 40 years has strong support been obtained for the idea that all mental functions are localizable to specific areas of the brain. But, it also has become clear that complex mental functions require integration of information from several cortical areas.

In the 1870s John Hughlings Jackson, the founder of modern British neurology proposed that the cortex is organized hierarchically and that some cortical areas serve higher-order integrative functions that are neither purely sensory nor purely motor, but associative. These higher-order areas of cortex, which we now call *association areas*, serve to associate sensory inputs to motor response and perform those mental processes that intervene between sensory inputs and motor outputs. The mental processes that Jackson attributed to these areas include interpretation of sensory information, association of perceptions with previous experience, focusing of attention and exploration of the environment.

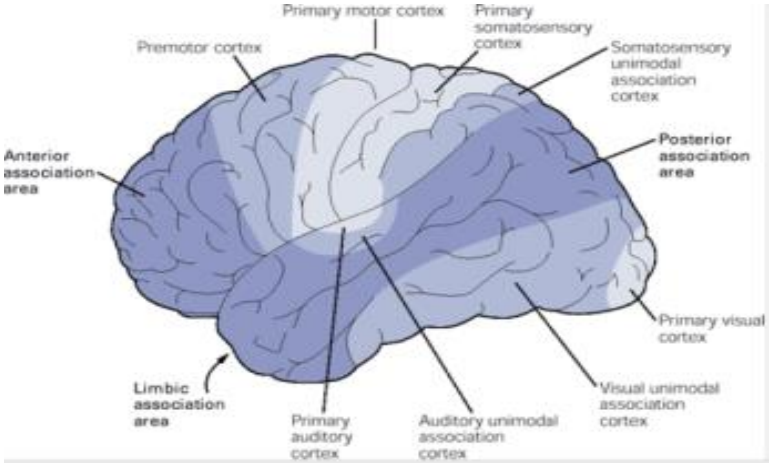

Fig.2:The association cortices occupy large areas on the exposed surfaces of the brain[21]

The association areas are capable of mediating complex cognitive processes because they receive information from different higher-order sensory areas and convey the information to higher-order motor areas that organize planned actions after appropriate processing and transformation.[21]

D. BASIC COGNITIVE FUNCTIONS

Cognitive functioning is comprised of multiple cognitive domains, such as memory, information-processing speed, language, visuoconstruction, perception, attention, and executive functions, which can be impaired selectively. A neuropsychological examination is well-suited to examine these domains in detail and to detect relatively modest impairments in individual persons.[14]

i. Attention

Attention is a basic but complex cognitive process that has multiple sub-processes specialized for different aspects of attentional processing. Some form of attention is involved in virtually all other cognitive domains, except when task performance has become habitual or automatic. The divisions are:

Selective attention refers to the ability to attend to some stimuli while disregarding others that are irrelevant to the task at hand.[22,23] Thus, deficits found in many of these tasks can be largely attributed to a general slowing of information processing in older adults rather than to selective attention deficits per se.

1.Divided Attention and Attention Switching:

Divided attention has usually been associated with significant age-related declines in performance, particularly when tasks are complex. Divided attention tasks require the processing of two or more sources of information or the performance of two or more tasks at the same time.[24]

2.Sustained Attention:

Sustained attention refers to the ability to maintain concentration on a task over an extended period of time. Typically, vigilance tasks are used to measure sustained attention, in which people must monitor the environment for a relatively infrequent signal, such as a blip on a radar screen. In general, older adults are not impaired on vigilance tasks.

ii. Working Memory

Working memory is a multidimensional cognitive construct that has been hypothesized as the fundamental source of age-related deficits in a variety of cognitive tasks, including long-term memory, language, problem solving and decision making. In fact, the majority of theories of cognitive aging seem to implicate working memory.[25,26,27]

Short-term or primary memory, on the other hand, involves the simple maintenance of information over a short period of time.

1Theories of Working Memory

Three theories of cognitive aging have been articulated within the context of working memory deficits, although they may apply more broadly across other cognitive domains: (1) one theory proposes a reduction of attentional resources, (2) one focuses on reduced speed of information processing, and (3) one ascribes problems to a failure of inhibitory control.[28]

a. Attentional Resources

Theories of age-related decline in working memory generally assume some reduction in processing resources. Craik and colleagues have suggested that the resource limitation is attentional and reflects a reduction in mental energy.[29,30]

b. Speed of Information Processing

Salthouse has suggested that speed of processing might be considered a resource and that age-related deficits in working memory and other cognitive tasks can be explained in terms of a general slowing of information processing.[31]

c. Inhibitory Control

Hasher, Zacks, and May proposed that a lack of inhibitory control might account for cognitive deficits associated with aging.[32,33]

iii. Long-Term Memory

Long-term memory, unlike short-term and working memory, requires retrieval of information that is no longer present or being maintained in an active state. This information could have occurred a few minutes ago or been acquired many years ago.

1Episodic Memory

Episodic memory refers to memory for personally experienced events that occurred in a particular place and at a particular time. This kind of memory allows one to think back through subjective time.[34]

2 Semantic Memory

Semantic memory refers to one's store of general knowledge about the world, including factual information and knowledge of words and concepts. Normally aging older adults do not have significant impairments in semantic memory. In fact, their knowledge of the world often exceeds that of young people. Semantic memories are believed to be stored in a variety of regions in posterior neocortex..[35]

3 Autobiographical Memory

Autobiographical memory involves memory for one's personal past and includes memories that are both episodic and semantic in nature. The bulk of the evidence suggests that recent memories are easiest to retrieve, those from early childhood are most difficult to retrieve, and there is a monotonic decrease in retention from the present to the most remote past, with one exception. Events that occurred between the ages of 15 and 25 are recalled at a higher rate.[36]

4 Procedural Memory

Procedural memory refers to knowledge of skills and procedures such as riding a bicycle, playing the piano, or reading a book. These highly skilled activities are acquired more slowly than episodic memories through extensive practice. Once acquired, procedural memories are expressed rather automatically in performance and are not amenable to description. Procedural memory depends on several brain regions,

including the basal ganglia and the cerebellum.[37]

5 Implicit Memory

Implicit memory refers to a change in behavior that occurs as a result of prior experience, although one has no conscious or explicit recollection of that prior experience.[38]

6 Prospective Memory

Much of what we have to remember in everyday life involves prospective memory — remembering to do things in the future.[39]

iv. Perception

Perception is a domain that encompasses the ability to process information coming from our senses, which can be visual, auditory, tactile, or chemical (smell and taste).[7]

HIGHER-LEVEL COGNITIVE FUNCTIONS

Speech and Language

Speech and language processing are largely intact in older adults under normal conditions, although processing time may be somewhat slower than in young adults. In fact, there is evidence that discourse skills actually improve with age. Older people often tell well- structured elaborate narratives that are judged by others to be more interesting than those told by young.[40]

Decision Making

Relatively little research has been done on the effects of aging on decision-making. Decision-making seems to be a domain that makes clear demands on processing resources, but in everyday life those demands may be reduced by life-relevant knowledge or expertise in the problem-solving domain.[41]

Executive Control

In the past decade, there has been an increasing focus on executive control as a primary contributor to cognitive decline with age. Executive control is a multi-component construct that consists of a range of different processes that are involved in the planning, organization, coordination, implementation and evaluation of many of our nonroutine activities. This so-called central executive plays a key role in virtually all aspects of cognition, allocating attentional resources among stimuli or tasks, inhibiting distracting or irrelevant information in working memory, formulating strategies for encoding and retrieval, and directing all manner of problem-solving, decision-making and other goal-directed activities.[42]

MEASURING COGNITION IN DIABETES:

When patients with diabetes are compared with non-diabetic controls, effect sizes for the differences in performance between the groups are generally small. This indicates that an optimal test battery should be very sensitive to be able to detect small changes in cognitive function and should not suffer from ceiling effects. Cognitive domains that are generally sensitive to brain dysfunction are speed of information processing and executive function, both requiring either fast or effortful processing. Furthermore, the impact of confounding factors should be kept to a minimum. In

diabetes, potentially confounding factors are peripheral neuropathy and retinopathy. Moreover, diabetics with cognitive complaints are more likely to be older, so tests should be selected that have been designed for use in older participants. Since type 2 diabetes is also related to socioeconomic status, low education (or even illiteracy), these factors should also be considered. Since diabetes is also associated with a higher risk of developing dementia in older patients, a test battery should also be sensitive to the pattern of deterioration that is typical for dementia. If a screening instrument for dementia is considered, the test's sensitivity and specificity should be considered.[7]

Summary of cognitive domains, psychological functions, and examples of tests that can be used for the assessment of patients with diabetes 7

Domain or function	*Brief description*	*Example of tests*
Intelligence	Premorbid academic functioning (crystallized intelligence) and actual problem-solving ability (fluid intelligence)	WAIS-IV; KAIT; Raven's Progressive Matrices; NART
Long-term memory and learning	The ability to acquire new information or to retrieve previously stored information, either related to personal memories (episodic) or general knowledge (semantic)	RAVLT; CVLT; HVLT; Benton Visual Retention Test; Location Learning Test; WMS-IV
Working memory	The capacity to actively maintain and manipulate information for a brief period of time (seconds to minutes), includes short-term memory	Digit span; Corsi-Block Tapping Task
Executive function	The planning, monitoring, initiation, shifting, and inhibition of behavior	Trail Making Test; Tower of London test; Wisconsin Card Sorting Test; BADS
Attention, concentration, and speed of information processing	Selection of relevant information, dual tasking, sustaining a state of alertness, and the "mental speed" with which information is processed	Reaction-time tests; Digit Symbol Substitution Test; PASAT; d2 Test; Continuous Performance Task
Praxis and motor function	Cognitive processes that underlie basic motor functions and complex actions	Pegboard tests; behavioral testing
Language	Communication skills, understanding others, and verbal expressing	Boston Diagnostic Aphasia Battery; Token Test; Verbal Fluency Tests
Perception	Both low-level and higher-order processing of visual, auditory, and tactile stimuli	Ishihara Test for Color Blindness; CORVIST; VOSP; Benton Test of Facial Matching
Overall cognition	Screening for cognitive decline regardless of cognitive domains	MMSE; CAMCOG-R; Mattis DRS-2
Mood	Symptoms of depression	BDI-II; HADS; GDS
Psychological complaints and coping	Complaints related to psychological distress as experienced by the patient and style of dealing with these	SCL-90-R; CFQ; PAID
Personality	Stable characteristics or traits that vary between individuals	NEO-PI-R

Assessment of evoked potential latencies is a common tool in neurophysiological studies of central nervous system involvement in patients with diabetes. Evoked-potential measurements can also be used to monitor CNS involvement in experimentally diabetic rodents. Such measurements allow monitoring of the course of development of CNS abnormalities or the effects of therapeutic

intervention.[43]P300 latency is considered an electrophysiological index of the relative timing of the stimulus evaluation process and cognitive impairment in recent years.[9,10]

E. EXPERIMENTS OF COGNITION:

Research on the neurobiology of the moral emotions in moral reasoning

A famous accidental experiment: Phineas Gage

One of the earliest and most famous "experiments" involves the accidental injury of railway foreman Phineas Gage late last century. On September 13, 1848, an accident sent a dynamite tamping iron through (among other structures) Gage's prefrontal cortex in both hemispheres (see Figure 3). It is reasonable to infer that the ventral and medial areas of Gage's prefrontal lobes were all but destroyed. Following the accident, Gage was a changed man; he became unreliable at work and eventually became a homeless drifter and alcoholic. His motor control and sensory perception, however, were normal, so far as the evidence shows. While it is difficult to know exactly what parts of Gage's brain were damaged, we do know that his social behavior changed dramatically following the accident. Later research revealed this was most likely due to bilateral damage to his prefrontal cortex caused by the passage of the rod. The Gage case is important because it provoked study on the role of the frontal structures in temperament and self-control and suggested a link between reasoning and the emotions.

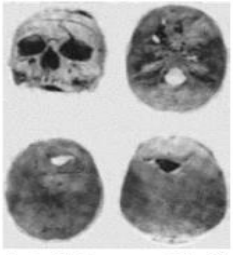

Figure 3 Gage's skull. Courtesy of the Warren Museum.

Lesion studies of humans with focal brain damage as well as experimental focal lesions on monkeys have demonstrated a relationship between prefrontal tissue and planning, decision-making, emotion, attention, memory for spatial and temporal patterns, and recognition of a mismatch between intent and execution.[19]

EXPERIMENTAL STUDIES OF PREFRONTAL LOBE:

RESULTS OF ABLATION:

Some of the more striking consequences of ablation of the prefrontal areas in monkeys are summarized below.

1) Alterations of activity:

   In the monkey, prefrontal ablations, especially those involving area 13 (on the orbital surface) produce initially a state of apathy: the animal sits with a blank expression on its face, the head is drooped and it stares into space ignoring the approach of human beings; such movements as are carried out are sluggish.

2) Alterations in emotional exteriorization:

   Monkeys were trained to discriminate between weights; when they chose the heavier weight correctly they were suitably rewarded. The postcentral gyrus was then extirpated, with the result that discrimination was grossly impaired.

3) Alterations in social behaviour:

   Unilateral or bilateral ablation of the rostral part of the cingular gyrus was immediately followed by marked changes in social behaviour. The monkey lost its preoperative shyness and fear of man. In a large cage, with

other monkeys, it showed no grooming or acts of affection towards its companions.

4) Impairment of memory:

The monkey was shown two inverted cups and food was placed under one of them; the monkey was trained to raise the cup covering the food; if it chose correctly it was given the food to eat.

5) Impairment of learning capacity:

Frontal lobe ablation in monkeys and man is followed by an impairment of learning capacity and of other purely intellectual functions.

6) Results of stimulation:

The prefrontal areas by their connections with hypothalamus and also by their direct brain stem connections can influence autonomic activities.[44]

F. COGNITIVE IMPAIRMENT:

Cognition includes memory, language, orientation. judgment, conducting interpersonal relationships, performing actions (praxis) and problem solving. Cognitive disorders reflect disruption in one or more of the above domains, and are also frequently complicated by behavioral symptoms.[45]

SYMPTOMS AND CHARACTERISTICS:

The symptoms and characteristics of cognitive impairment depend on the specific type of impairment. The most common symptoms and characteristics include:

- avoidance of eye contact
- difficulty understanding the motivation, perspectives or feelings of others
- difficulty coping with changes

- decreased ability to learn new skills
- difficulty with reading, writing, spelling and comprehension
- co-ordination problems.[46]

CAUSES OF COGNITIVE IMPAIRMENT:

Congenital causes of cognitive impairment:

Chromosomal abnormalities such as Down syndrome, fragile X syndrome, cri du chat syndrome, Prader-Willi syndrome, and others, Congenital hypothyroidism (underactive thyroid)

Birth-related causes of cognitive impairment:

Cognitive impairment can also be caused by complications related to delivery including: Infection, Lack of oxygen during labor or birth, Preterm birth or its complications such as intracranial hemorrhage (uncontrolled bleeding in the brain)

Causes of cognitive impairment that occur after birth or during childhood and adolescence

Autism (abnormal development of communication and social skills),Head injury. Heavy metal poisoning such as lead poisoning

Causes of cognitive impairment that occur in adults:

Alcohol or drug abuse, Brain or spinal cord injury, Diabetes mellitus

Serious or life-threatening causes of cognitive impairment:

Brain tumor, Encephalitis (inflammation and swelling of the brain due to a viral infection or other causes) **.**[47]

G. **DIABETES MELLITUS:**

Diabetes mellitus is an endocrine disorder of carbohydrate metabolism resulting from inadequate insulin release (insulin dependent diabetes mellitus, or type 1 diabetes; T1D) or insulin insensitivity (non-insulin-dependent diabetes mellitus, or type 2 diabetes; T2D), both of which result in hyperglycemia if uncontrolled.[48]
Diabetes mellitus can lead to many complications particularly when untreated. The association between type 2 diabetes mellitus and dementia has been of great interest, and this is particularly relevant with the increase in prevalence of both diabetes and dementia with increasing life expectancy. [49,50,51]

Manifestations of diabetes-induced CNS complications may include structural alterations or brain atrophy, as well as changes in electrophysiological properties that ultimately result in deficits in cognitive performance.T2D may be triggered or worsened by a number of factors including obesity, hypertension and other features of the metabolic syndrome.

Additional factors that may contribute to diabetes-induced cognitive impairment include disrupted insulin signaling and glucose homeostasis in the CNS.
Under normal circumstances glucose is the predominant metabolic fuel source of the adult brain and is transported to the CNS from the periphery via facilitative glucose transporters. Since the brain can neither synthesize nor store glucose for extended periods of time, it is essential that proper glucose regulation be achieved in the periphery to ensure appropriate glucose transport to the CNS, processes that may be

disrupted in poorly-controlled diabetes.

Many brain structures, such as the hippocampus, are extremely sensitive and responsive to changes in glucose homeostasis. Additionally, glucose and insulin are both instrumental regulators of cognitive function, further supporting the hypothesis that inefficient regulation of these two factors may contribute to cognitive deficits in diabetes phenotypes.[48]

H. THE RELATIONSHIP BETWEEN COGNITIVE DECLINE AND DIABETES:

In a comprehensive review of literature on the association between impaired glucose tolerance, type 2 diabetes and cognitive function, it was concluded that the most consistently reported measures were impairment in verbal memory and processing speed, with preservation of functions in other areas including visuospatial function, attention, semantic memory and language.[52]

Potential risk factors for cognitive impairment in type 2 diabetes are:

Acute and chronic hyperglycaemia

Macrovascular disease

Microvascular disease

Hypertension

Hyperinsulinaemia

Glucocorticoid excess

Elevated inflammatory markers

Recurrent severe hypoglycaemia

Depression

Drug therapies

Genetic factors

Hyperglycaemia is the hallmark of all types of diabetes and could cause cognitive decrements by several different mechanisms. Acute changes in blood glucose are known to alter regional cerebral blood flow and could also cause osmotic changes in cerebral neurones.

The recognized association between type 2 diabetes and macro- and microvascular disease is pertinent to the pathogenesis of dementia. The former could cause cognitive impairment because of the increased incidence of embolic stroke.[53]

The effects of T2D upon cognitive function are due to insulin resistance. Additionally, insulin resistance is associated with a host of conditions including, hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia and increased central adiposity collectively termed the metabolic syndrome.[48,53] Many features of the metabolic syndrome may contribute to cognitive impairment independently or in combination with one another.[48]

Other factors

There are other reasons why people with type 2 diabetes may be more at risk of developing dementia than the non-diabetic population. Depression is more common in people with type 2 diabetes and is itself associated with cognitive impairment. It is not clear whether the association between type 2 diabetes and depression is related to a specific biological mechanism or simply because depression is more common in people who have chronic medical disorders, in general.[53]

Inflammation

The development of macrovascular disease is now recognized to involve inflammatory processes, although it is still uncertain whether inflammation has a causal effect on cardiovascular disease or whether it is a consequence of atherosclerotic processes. More recently, it has been hypothesized that inflammation

may also play a role in the development of dementia and/or cognitive impairment. Animal studies suggest that 'over-production' of cytokines in the brain is associated with neurodegeneration and cognitive deficits, while in humans, inflammation occurs in the brain of AD sufferers.[53,54]

I. PATHOPHYSIOLOGY OF COGNITIVE DYSFUNCTION:

Proposed pathogenetic mechanisms of cognitive dysfunction in diabetes include chronic hypoglycemia, vascular disease, cumulative effect of hypoglycemic events and possible direct effects of insulin on the brain.

POTENTIAL CONTRIBUTORS TO DIABETES-INDUCED BRAIN AGING:

1. INSULIN AND GLUCOSE

Peripheral glucose metabolism and insulin sensitivity are key determinants of cognitive functioning in aging.[55]The discovery of centrally located insulin receptors has lead to a greater appreciation of the multi-faceted functions of insulin within the CNS. The expression of insulin receptors in the hippocampus has driven the hypothesis that insulin is an important contributor to or regulator of cognitive function a theory supported by clinical evidence.[2,48,53]

For example, chronic intranasal insulin administration improves cognitive performance in both Alzheimer's disease (AD) and non-demented individuals and acute insulin administration has been shown to improve declarative memory in AD patients. Insulin also modulates basal synaptic transmission and restores normal synaptic plasticity in the hippocampus of animal models of diabetes.Studies suggest that decreases in insulin receptor (IR) activity may be an initiating factor producing deficits in hippocampal plasticity and ultimately cognitive decline.

Another important contributor to brain function, especially as it relates to cognition, is glucose. In this regard, fasting plasma glucose levels were negatively correlated with episodic memory and recall in a study of normal healthy women.[48,54] On the other hand, the most recent findings indicate that cerebral insulin improves cognitive processes and memory, especially hippocampus-dependent declarative memory.[2]

Also, glucose administration improves cognitive performance in people and animals irrespective of pre-existing cognitive impairments. During hippocampal-dependent cognitive tasks, extracellular levels of glucose are decreased in the hippocampus of rodents, implying increased glucose uptake and utilization by cells. The intimate connection between glucose and cognition reinforces the importance of maintaining the delicate balance of glucose levels within the brain.[48]

2. Advanced glycation end products and oxidative stress

In addition to altering cognitive performance, poor glycemic control increases the accumulation of advanced glycation end products (AGE), products formed by the non-enzymatic reaction between sugars and amino groups, and oxidative stress in the brain, which may lead to cellular and molecular damage. In this regard, AGE and oxidative stress have both been identified as potential contributors to diabetes-induced brain aging.[48,54]

3. HPA axis dysfunction

Many pathological conditions are associated with hypothalamic– pituitary–adrenal (HPA) axis dysregulation, including diabetes. The relationship between glucocorticoids (GCs) and obesity, a common feature in T2D patients, is relevant in terms of induction of insulin resistance. Emotional stressors, like depression, activate the other part of limbic areas – amygdala. Activation of amygdala caused chronic

elevation in cortisol levels, which is known as a stress hormone. In this sense, lipolysis induced by GCs increases free fatty acid levels in blood, which in turn causes hyperglycemia through the stimulation of hepatic gluconeogenesis and a reduction in glucose uptake by competing with glucose for oxidation. Consequently, a compensatory increment in insulin secretion leads to hyperinsulinemia, downregulation of insulin receptors and insulin resistance.[2,48,53]

4. Obesity

Since there is a positive correlation between risk of T2D development and obesity , understanding the relationship between obesity and cognitive function is an important health care issue. In this regard, obesity has been both positively and negatively correlated with dementia in older individuals .[48,54]

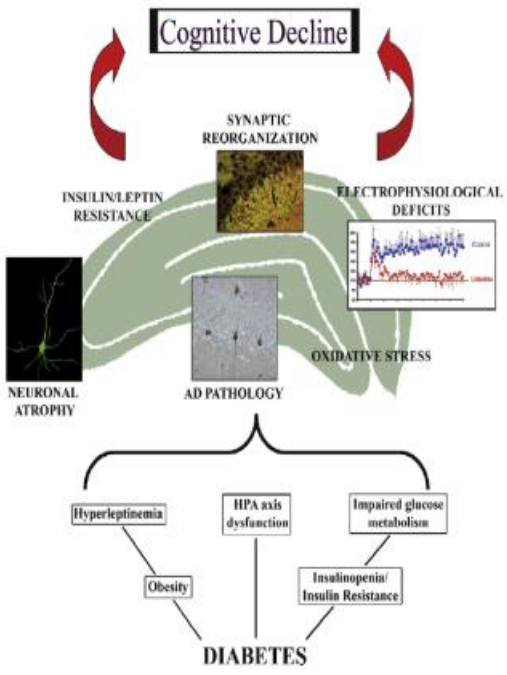

Fig.4: Potential mechanistic mediators of diabetes-induced brain aging[48]

J. EVOKED POTENTIALS:

These are electrical manifestation of the brains reception of and response to an external stimulus. Pattern shift visual, brainstem auditory and short-latency

somatosensory evoked potentials are reliable diagnostic tests that yield reproducible results in routine clinical practice. The clinical utility of evoked potentials is based on their ability (1) to demonstrate abnormal sensory system function when the history and/ or neurologic examination are equivocal; (2) to reveal the presence of clinically unsuspected malfunction in a sensory system when demyelinating disease is suspected because of symptoms and signs in another area of the central nervous system; (3) to help define the anatomic distribution of a disease process and (4) to monitor changes objectively over time in a patients status. These tests provide sensitive, quantitative extensions of the clinical neurologic examination. They primarily afford numerical data; sometimes the absence of a wave or an abnormal configuration of its potential field also provides useful information.

P300 – NORMAL WAVEFORMS AND THEIR GENESIS:

The positive and negative waveforms are designated as P and N, respectively. There are two negative (N_1, N_2) and two positive (P_2 and P_3) waves. These are labeled by their average latency in normal individuals, that is, P_3 appears around 300ms after the stimulus. Precise measurement of P_3 latency and amplitude is difficult because of its variable morphology and broad configuration. P_3 is composed of two components: P_{3a} and P_{3b} . Ideally, both the components should be measured although in clinical practice only P_3 measurements are done. There are two ways of measuring P_3 latency:

1) Point of maximum P_3 amplitude

Intersectional extrapolation-the ascending and descending limbs of P_3 are extended to the point of intersection, which is measured as P_3 latency.[56,57]

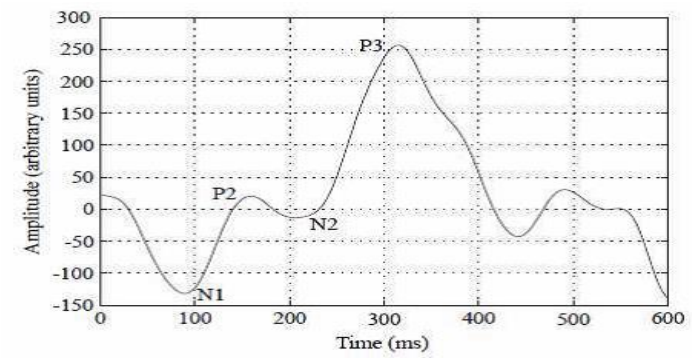

Fig.5: Normal P300 waveform

The normal values of different waveforms of cognitive evoked potential are as follows:[56]

WAVEFORMS	LATENCY(MEAN±SD) ms	AMPLITUDE(MEAN±SD) μV
CZ N1	102.0±16.9	9.3±3.5
P2	172.1±20.0	3.6±2.5
N2	232.1±39.2	7.3±4.1
P3	346.9±38.1	9.2±5.0
FZ P3	346.5±38.0	6.6±3.6
PZ P3	346.2±41.1	9.6±3.8

Peak latency, base-to-peak amplitude

GENERATORS OF P300:

The exact origin of P300 is still not known. Different areas of brain such as inferior parietal lobule, frontal lobe, hippocampus, medial temporal lobe, insula, and other limbic structures have been reported to contribute to scalp recorded P300. Despite suggestion regarding the generation of P300 by medial temporal lobe and hippocampus, later studies have disproved the role of medial temporal lobe by demonstrating the presence of P300 in patients with temporal lobectomy or bilateral hippocampal and temporal lobe lesions.

Recent studies employing fMRI and magnetoencephalography have been utilized to study the generators of P300. Combined ERP and fMRI study, P300 was attributed to frontal area and insula, whereas P_{3b} to parietal and inferior temporal areas; thus pointing to the involvement of distinct attentional subsystems in target and distracter processing.[62]

K. VARIABLES AFFECTING P300:

A number of variables may affect P3 latency and amplitude, hence they require careful attention to avoid misinterpretation.

1. ATTENTION:

The subject must be awake and alert to obtain the P3. There are a series of related variables that affect the P3: level of attention, alertness, and response accuracy. Decreasing alertness, Drowsiness or inattention are associated with a decrease in the amplitude of some cortical EPs. While an altered P3 may still be present in stage 2 sleep, it is obliterated in slow wave sleep.[57]

2. TASK:

The specific task that is given to the subject will affect the P3. In the oddball paradigm, when a subject is instructed to specifically attend to the rare stimulus, the P3 amplitude increases. An identical rare stimulus to which the subject is not told to attend will elicit a lower-amplitude response. The latency increases as the discrimination of task becomes harder.[57]

3. AGE:

The P 3 latency increases with increasing age.[62] There is an increase in mean latency by about 1-1.5 ms/year after the age of 20 years. The regression line for age and P3 latency has been found by some researchers to increase in slope with

increasing age, although others have not found this. Some of the variability across studies may relate to failure to control for perceptual thresholds in the elderly which may impact on the P3 and to control for the specific task [i.e., a two-tone oddball versus a three-tone target, rare and frequent tone task.[57]

4. DRUGS:

Drugs have variable effect on P3. Anticholinergics and antihistaminics increase P 3 latency and reduce its amplitude. On the other hand, physostigmine, a cholinesterase inhibitor can reverse the effect of anticholinergic on P3. Methylphenydate, amphetamine, antiserotonergic, anticonvulsants (phenytoin, carbamazepine, phenobarbitone) have very little effect on P3. L-DOPA reduces the latency of P3 in Parkinson's disease patients, but has no effect in normal individuals.[57]

5. TECHNICAL PARAMETERS:

Stimulus intensity generally does not influence P3; however, on markedly high intensity P 3 latency may be reduced. P3 amplitude increases as the target stimulus frequency in the global sequence decreases. Another important variable is local sequence probability. A target stimulus that is preceded by another target stimulus results in comparatively low amplitude P3 than if it is preceded by a nontarget stimulus.[56]

6.INTRAINDIVIDUAL VARIABILITY:

Like any other neurophysiological test, P3 also has certain variation in the same individual. In a study of nine individuals there was 18 ms difference in P3 latency in two consecutive trials and 12 ms difference when the trials were carried out 2-4 weeks apart. On the other hand, in a larger study on 100 subjects, there was no statistically significant difference in P3 latency and amplitude in the first and second trial.[56]

7.FOOD INTAKE:

Food intake increases the amplitude of the target stimulus P3 ERP component elicited with auditory stimuli, although the influence on peak P3 latency appears minimal –at least for the ERP measurements and experimental task conditions employed in the present studies.[58]

8.BIOLOGICAL RHYTHMS INFLUENCE P300 :

Recent studies have provided evidence that the P300 also is influenced by biological processes such as fluctuations in the arousal state of subjects. Earlier studies have shown that natural (circadian, ultradian, seasonal, menstrual) and environmentally induced (exercise, fatigue, drugs) state variables influences P300. Mental performance is known to vary with time-of-day, although the effects depend on a mix of physiological and cognitive factors as well as individual differences. The general influences of time-ofday on specific ERP components have been reviewed previously. The Endings suggest that just as the behavioral sequelae stemming from physiological variation originating with circadian rhythms are imprecisely understood, how time-of-day contributes to ERP variation also is unclear. This conclusion derives from the weak effects of day-time circadian variation for P300 and electroencephalographic (EEG) measures.[59]

L. CLINICAL APPLICATIONS OF P300 RECORDING:

AGING:

P3 latency increases and amplitude decreases with advancing age. Visuospatial memory task recognition evaluated in young (20-29 years) and old (60-82 years) revealed significantly slower reaction time in the elderly. P3 amplitude was significantly lower in the elderly. Significantly slower reaction time and low P3

amplitude suggest visuospatial slowing in the elderly. P3 may be a useful technique for documenting age-related cognitive changes.[56]

DEMENTIA:

In dementia, prolongation of P3 latency compared to normal has been reported. The frequency of abnormality has ranged between 30% and 80%. P3 may be helpful in differentiating behavioral abnormalities in dementia and those because of psychiatric disturbances. P3 is expected to be normal in psychiatric patients as opposed to patients with dementia. There have been many studies with differing results on the role of P3 in the diagnosis of dementia . In the early stage of dementia, the P3 may be normal or marginally altered, which undermines the value of P3 as a clinical diagnostic test of dementia.[56]

MOVEMENT DISORDERS:

In Parkinson's disease (PD) associated with dementia, P3 latency has been reported to be prolonged compared to nondemented PD patients. Neuropsychological tests in multisystem atrophy (MSA) have revealed frontal lobe dysfunction. Visual ERP and MRI studies have revealed significant prolongation of P3 latency, reaction time and reduction of P3 amplitude in MSA compared to normal. P3 latency in MSA correlated with cerebellar and pontine atrophy. In another study, novelty P3 and target P3 latencies were significantly prolonged and amplitude reduced in MSA. There was significant negative correlation between P3 latency and degree of postural hypotension, which was attributed to frontal lobe dysfunction.[56]

HIV INFECTION:

Patients with HIV infection often complain of cognitive disturbance, which may be due to AIDS dementia complex, HIV-associated encephalopathy or due to CNS opportunistic infections. In asymptomatic HIV patients there is a low frequency

of P3 abnormalities, which may range from 0% to 30%. The P3 abnormality inversely correlated with CD4 count.[56]

PSYCHIATRIC DISORDERS:

Abnormality in thought process and cognitive functions occur in many psychiatric disorders. There are several studies evaluating the role of ERP in psychiatric disorders. In schizophrenia, P3 has been evaluated in acute attack, chronic stage as well as to monitor the effect of treatment. Reduction of P3 amplitude in schizophrenia compared to controls has been reported.[56]

MENTAL RETARDATION:

In mental retardation due to various causes .P3 latency and amplitude have been studied but have not revealed a consistent pattern. In Prader-Willi syndrome there is attenuation of P3. Similar results have been found in Down syndrome and Turner syndrome. Following transdermal nicotine injection, P3 latency is reduced and amplitude increased in Down syndrome suggesting its possible therapeutic role.[56]

NUTRITIONAL,TOXIC AND METABOLIC DISORDERS:

Nutritional deficiency, especially during early childhood, has raised controversy about future cognitive development. In a study on nutritionally deprived children during early childhood, MRI and cognitive evoked potential studies were conducted. There was significant increase in anterior-posterior hemispheric asymmetry. P3 latency was normal but the amplitudes of P2 and P3 were higher in the undernourished children compared to controls. There have been reports of changes in P3 in metabolic and toxic encephalopathies. In renal failure and hepatic encephalopathy prolongation of P3 latency has been reported.[56]

SCHIZOPHRENIA:

Multiple investigators have reported a lower-amplitude P3 or P3b in groups of schizophrenics compared to controls. Most of these studies have not reported a change in P3 latency. It has been postulated that there is an alteration of P3 topography in schizophrenia.[57]

PEDIATRIC AND CONGENITAL DISEASES:

Finley and colleagues (1985) studied the utility of cognitive EP testing in 243 children and found a high correlation between prolonged P3 latencies and evidence of "organicity" on clinical grounds, Halstead-Reitan neuropsychological assessment, and low MMSE scores. One study of mentally retarded children found altered long-latency potentials and slow potentials.[57]

OTHER BEHAVIORAL NEUROLOGY:

The P3 and other long-latency EPs have been used to investigate the pathophysiology ofvarious neurobehavioral syndromes. These include prosopagnosia, inattention following prefrontal lesions, visual neglect following unilateral parietal lobe lesions, anosognosia, "blindsight", closed head injury transient global, and other memory. Patient's with Korskaoff's syndrome did not have any alteration in their P3.[57]

LIE DETECTION:

Since the mid 1980s, one of the most discussed uses of ERPs such as the P300 is related to lie detection. In a proposed "guilty knowledge test"—a subject is interrogated via the oddball paradigm much as they would be in a typical lie-detector situation. The technique relies on reproducible elicitation of the P300 wave, central to

the idea of a Memory and Encoding Related Multifaceted Electroencephalographic Response (MERMER) developed by Dr. Lawrence Farwell.[60]

BRAIN-COMPUTER INTERFACING:

The P300 has a number of desirable qualities that aid in implementation of brain computer interfacing. First, the waveform is consistently detectable and is elicited in response to precise stimuli. The P300 waveform can also be evoked in nearly all subjects with little variation in measurement techniques, which may help simplify interface designs and permit greater usability. The speed at which an interface is able to operate depends on how detectable the signal is despite "noise." One negative characteristic of the P300 is that the amplitude of the waveform requires averaging of multiple recordings to isolate the signal. This and other post-recording processing steps determine the overall speed of an interface. It remains to be shown whether such systems provide similar results in patients suffering from locked-in syndromes, the main target population for such brain driven devices.[61,62,63]

METHODOLOGY

MATERIALS AND METHODS

SOURCE OF DATA

Subjects: Study group consisted of 30 diabetics attending the diabetic clinic and medical outpatient department in the RL Jalappa Hospital, Kolar and 30 age and sex matched controls.

Sample determination:

How large a sample would be needed for comparing 2 groups of subjects using

$\alpha=0.05$,

to detect a difference of d(mmse) =5 or more with power $=1-\beta=0.95$ is determined

using formula; $$N=n_1+n_2=\frac{4\sigma^2(Z_{1-\alpha/2}+Z_{1-\beta})^2}{d}$$

Similar studies referred show: MMSE d=5 or more; $\sigma=2$

P_{300} d=12 or more; $\sigma=6$

$Z_{1-\alpha/2}=1.96$, $Z_{1-\beta}=1.65(0.95)$

Sample size is 30 in each group

TYPE OF SAMPLING: Systematic sampling

Duration of study: December 2011 to February 2012

Every first patient coming to Diabetic OPD was recruited on 3 days a week. Monday,Wednesday,Thursday.

CONTROLS: Age and gender matched non-diabetic controls were recruited from SDUMC campus and RL Jalappa hospital.

METHOD OF COLLECTION OF DATA

Data was collected by administering MINI MENTAL STATE EXAMINATION (MMSE) questionnaire, by estimating auditory threshold by pure tone audiometer and by recording P300 Latency from subjects after obtaining informed consent for the study. Ethical clearance was also obtained from Institutional Ethical Clearance Committee for the study.

CRITERIA FOR SELECTION OF STUDY (DIABETIC) GROUP:

Inclusion criteria:

1. MMSE score more than 25.
2. Age above 40 years.
3. Type 2 diabetes with duration of diabetes more than 2 yrs.
4. Fasting blood sugar level more than 126 mg/dl.
5. No previous history of neurological events, cardiovascular complications.
6. No hearing loss on audiometry.

. Exclusion criteria:

1. The use of medications as sedatives, antidepressives or neuroleptics.
2. Subject with history of recent infectious disease like meningitis, encephalitis.
3. Blindness, stroke, Alzheimer disease and psychiatric disorder.

CRITERIA FOR SELECTION OF CONTROL GROUP:

INCLUSION CRITERIA:

1. MMSE score more than 25.
2. Age above 40 years.
3. No hearing loss on audiometry.

EXCLUSION CRITERIA:

1. Non-diabetics.
2. The use of medications as sedatives, antidepressives or neuroleptics.
3. Subject with history of recent infectious disease like meningitis, encephalitis.
4. Blindness, stroke, Alzheimer disease and psychiatric disorder.

METHODOLOGY

A questionnaire was filled by the subjects recruited for the study consisting of characteristics like sex, age, duration of diabetes, medical history of hypertension, dyslipidemia and smoking.

MINI MENTAL STATE EXAMINATION(MMSE):

A standard MMSE score was administered to each subject. The MMSE scale ranged from 0 to 30 points with higher number indicating better performance. Instructions were identical for each subject. The MMSE consisted of 19 questions designed to assess the patient's mental status in the following 5 categories: 10 orientations questions, 2 memories items, 1 calculation item, 5 language items and 1 constructional item.

PURE TONE AUDIOMETER:

An audiometer is an electronic device which produces pure tones, the intensity of which can be increased or decreased in 5 dB steps. Air conduction Thresholds and measured for tones of 250, 500, 1000, 1500, 2000, 4000 6000 and 8000 Hz. Bone conduction thresholds and measured for 250, 500, 1000, 1500, 2000, 4000 hertz. The amount of intensity that has to be raised about the normal level is a measure of the degree of hearing impairment at that frequency. It is charted in form of a graph called the 'audiogram'. The thresholds of bone conduction are a measure of the cochlear function. The difference in the thresholds of air and bone conduction (A-B gap) is a

measure of a degree of conductive deafness. The audiometer is so calibrated that hearing of a normal person, both of air and bone conduction is at 0 dB and there is no A-B gap.

The method is based on American Society for Speech and Hearing Association [ASHA] 1978 guidelines for manual pure tone audiometry (PTA). The procedure is as follows.

1. The subject is made to wear earphones during air conduction testing and a vibrator during bone conduction testing. He is instructed to respond whenever and as soon as the tone comes on, regardless of how faint the tone is and to stop responding as soon as the tone goes off. The subject is also told that one ear is tested first and then the next ear is tested. A pulse of tone is presented at a set frequency and set dB hearing level using adjustment knobs on the audiometer.

2. Mode of response is by pressing button.

3. The response should not be considered as one, unless the latency of response is consistent and the subject responds appropriately to the termination as well as initiation of the tone.

4. Subjects should be reinstructed if false positive response (in the absence of a tone) or false negative (in the presence of a tone) are obtained. False positive responses can be minimized by varying the interval between audible stimuli, employing pulsed or warbled tones or by asking the subject to report the number pulsed tones given at a particular level.

5. The subject is familiarized with the tone by one of the two methods

a) The attenuation is set at low limits and the intensity is slowly and continuously increased until a response occurs.

The tone is presented at 30 dB hearing level and at 50 dB hearing level if no response

occurs at 30 dB. If there is no response even at 50dB, tone is increased in 10 dB steps until a response occurs.

6. The duration of tone is 1-2 seconds. The inter-stimulus interval is varied, but is never less than the duration of the stimulus.

7. After the first response, the tone is decreased by 10 dB whenever the subject responds and is increased by 5 dB if the person fails to respond.

'Threshold' is defined as the lowest intensity at which the subject responds at least half the time and at least three times on ascending runs.

8. The earphones should be so placed that the grid is directly over the entrance to the ear canal. Hair should be manipulated so that it is not trapped underneath the headphones and other obstacles such as earrings should be removed.

9. Diagnostic testing should be done at the following octave frequencies- 250, 500, 1000, 2000, 4000 and 8000 hertz, following the above steps each time.

The ambient noise at any octave frequency should be less than 25 dB.

The bone vibrator for bone conduction checking must be placed on the mastoid process, no closer than a thumb's width to prevent acoustic radiation and diagnostic testing at 250, 500, 1000, 2000 and 4000 hertz is done as above.

INTERPRETATION OF AN AUDIOGRAM:

Conductive deafness- is indicated by raised air conduction thresholds (25dB) and a normal bone conduction threshold with a wide air-bone gap of 15 dB or more.

Sensorineural deafness-is indicated by raised air and bone conduction thresholds (both>25dB) and the air bone gap does not exceed 10dB.

Mixed deafness- air and bone conduction thresholds are raised with air bone gap of > 15dB

DEGREE OF HEARING LOSS [WHO Classification 1980][64]

Normal	0-25 dB
Mild	26-40 dB
Moderate	41-55 dB
Moderately severe	56-70 dB
Severe	71-91 dB
Profound	>91 dB

Then P300 was recorded in all the subjects included in the study in whom audiometry was done. P300 was recorded in an electrically shielded room by using RMS EMG EP MARK 2 machine.

P300 :

P300 cognitive evoked potential was recorded using RMS EMG EP MARK 2 machine in all the subjects. The test was done in a silent room, with the individual comfortably sitting on a chair, instructed to remain alert, paying attention to the rare stimulus presented in a random fashion to the frequent stimulus (oddball paradigm), and count it.

Cognitive events requires attentional and immediate memory processes. This is a positive wave which occurs at the given latency of 250-500 ms. The P300 component is often elicited with a simple discrimination task known as the 'oddball' paradigm, since there are two stimuli, which are presented in a random series so that one of them occurs relatively infrequently that is, the oddball. The person has to discriminate between both of them covertly (mental counting).P300 is related to the neutral activity of the anterior cingulate.

Fig.6: Method of recording P300 Event Related Potential

SPECIFICATIONS OF RMS EMG EP MARK 2 MACHINE:

RMS EMG EP MARK 2 machine is a two channel evoked potential and EMG recording machine. RMS EMG EP MARK 2 has options of performing wide variety of tests such as Auditory Evoked Potentials (AEPs), Somatosensory Evoked Potential (SEP), Visual Evoked Potential (VEP) and P300 Event Related Potentials (ERP).

ELECTRODE POSITIONS:-

Ag/Agcl disk electrodes were affixed with electrode gel with reference electrode placed at Cz vertex scalp site, two active electrodes placed at mastoid processes (A1-A2). These active electrodes are linked .The ground electrode was placed at Forehead (FPz).

AMPLIFIER SETTINGS: Gain settings is 2μV/D; Low filter is 2Hz; High filter is 100Hz

STIMULUS CHARACTERISTICS:

300 sweeps are given at a sweep speed 50ms/div. Two different types of stimulus is given to the subject, one is low pitched frequent stimulus 750Hz Tone and other is high pitched rare stimulus 2KHz Tone.The Ramp cycles is set at 10 and Plateau cycles is set at 10. Depending on these settings software automatically handles the plateau cycles and ramp cycles of rare stimulus. Randomness of occurrence of rare stimulus is 20% which means that out of 100 stimulus, 80 was frequent stimulus and 20 was Rare stimulus. During test, subject was required to count rare stimuli. Responses from both the Rare and Frequent stimuli was recorded and averaged separately.

RECORDING CONDITIONS:-

The subjects were individually assessed in a sound attenuated and dimly lit cabin using RMS EMG EP MARK 2 machine.

RECORDING PROCEDURE:

The subjects were advised to come without applying oil to scalp. They were further instructed to shampoo and dry their hair. The skin was prepared by abrading and degreasing. The subjects were asked to avoid substances which would influence cognitive performance (ex. coffee, containing caffeine) for the day preceding and the day of recording, where this was unavoidable, the session was taken on other day. A trial session was given to rule out any hearing deficit.P300 evoked potentials were recorded while subjects sat erect on the chair with their gaze at a fixed point. The standard and target auditory stimuli were delivered through close fitting ear phones. The subjects were asked to distinguish between the two tones by mentally counting the 'target' stimuli. The P300 responses were recorded.

VARIABLES MEASURED:

The peak latency (ms) was defined as the time from stimulus onset to the point of maximum positive amplitude within the latency window. The peak latency was measured for potential recorded at Cz referred to linked mastoid processes.

DATA EXTRACTION:

Peak latencies of P300 responses at Cz vertex scalp site. Peak latency was measured as time from the stimulus onset to the point of maximum positive wave in the given latency of 250-450 ms.

The P300 latency thus obtained was correlated with the duration of diabetes and the test group results was compared with the control groups.

Statistical analysis: While comparing means- Independent student t test was done,

For quantitative data- Pearson correlation and for descriptive statistical analysis-mean and standard deviation was done.

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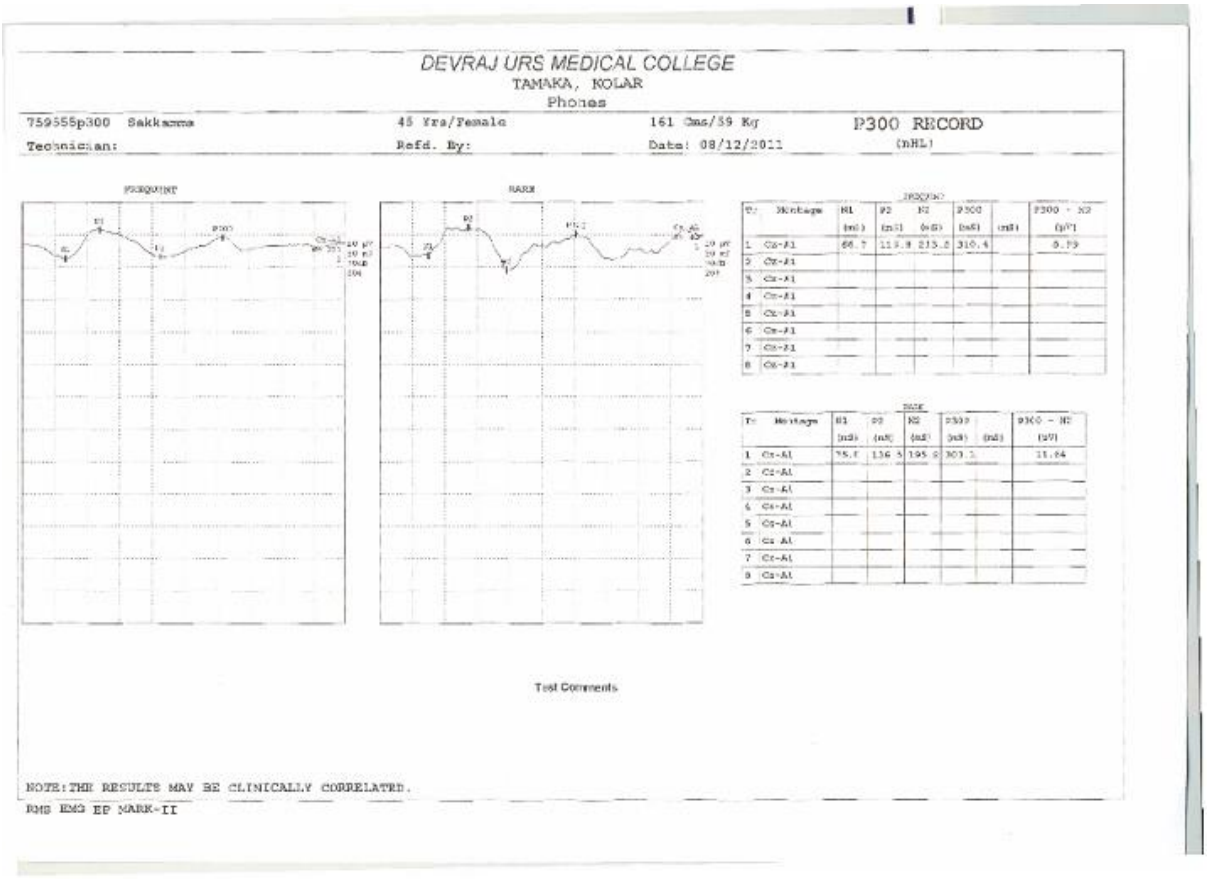


Fig.7: P300 waveform

RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

In the present study, 30 diabetics (study group) and 30 age and sex matched controls (non diabetics) were selected considering the inclusion and exclusion criteria. Pure tone audiometry (PTA) was done to screen for hearing loss and after hearing loss was ruled out, P300 recording was done on them. The data was analysed using appropriate statistical methods and discussed.

Presentation of data

Master chart showing P300 wave latencies and MMSE scores with age and sex of the subjects and their duration of diabetes in case of the study group. It also showed H/o hypertension, dyslipidemia and smoking.

Statistical Treatment of the data

The data was suitably arranged into tables for discussion under different headings. Descriptive statistical analysis was carried out on this data. Results on continuous measurements are presented as mean $\pm$ standard deviation and results on categorical measurements are presented in number %. Significance was assessed at 5% level of significance. P300 recording was compared between diabetics and age and sex matched controls and independent t test was done. The Pearson correlation between P300 Latency and duration of diabetes was done. To study the association of mean P300 latency levels among coexisting conditions like hypertension, dyslipidemia and smoking in diabetics, independent t test was done. Conclusions were drawn based on the outcome of this statistical treatment.[65,66]

TABLE 1: CHARACTERISTICS OF THE SUBJECTS

SUBJECTS	DIABETICS	CONTROLS
Total (n)	30	30
Female n(%)	8(26.66%)	8(26.66%)
Male n (%)	22(73.33%)	22(73.33%)
Age(Mean± SD) (years)	62.26± 7.98	62.26± 7.98
Duration of diabetes (Mean± SD) (years)	7.43±4.15	-
Hypertension (%)	43.33%	30%
Dyslipidemia (%)	26.66%	23.33%
Smokers (%)	40%	13.33%

CHARACTERISTICS OF THE SUBJECTS: as shown in **TABLE 1**, 60 subjects were selected. Study group comprised of 30 type 2 diabetics (22 males and 8 females), aged 62.26±7.98 years and with duration of diabetes of 7.43±4.15 years. The percentage of hypertensives was 43.33% and 30% in study and control group respectively. The percentage of dyslipidemia is 26.66% and 23.33% in study and control group respectively. The percentage of smokers was 40% and 13.33% in study and control group respectively.

TABLE 2: MMSE SCORES OF DIABETICS AND CONTROLS

Groups	Number of subjects	Mean MMSE score	Std. Deviation	t value	p value
DIABETICS	30	26.30	1.44	0.096	0.924
CONTROLS	30	26.26	1.22		

TABLE 2 shows MMSE scores of diabetics and controls. The average mean±SD MMSE score is 26.3 in study group and 26.26 in controls which showed no statistical difference with p value of 0.924.

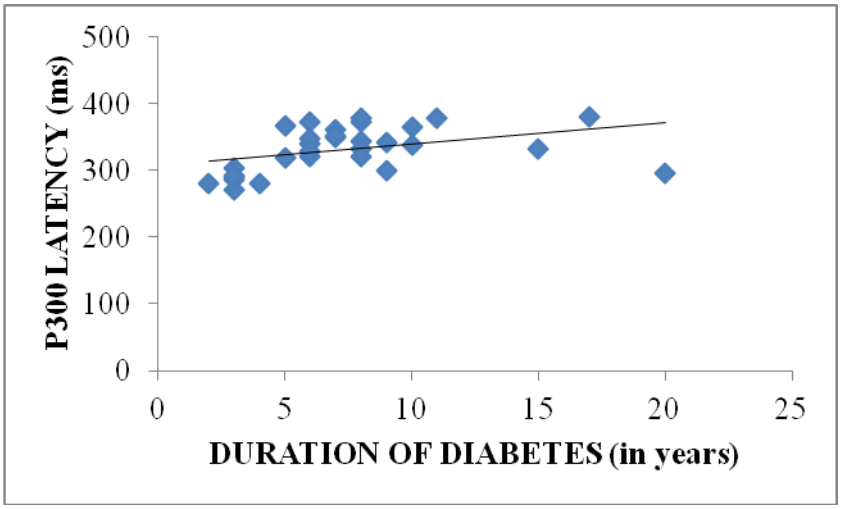
TABLE 3: P300 LATENCY VALUES (ms) OF DIABETICS AND CONTROLS:

Groups	Number of subjects	Mean P300 latency(ms)	Std.Deviation	t value	p value
DIABETICS	30	331.53	33.63	4.554	0.001**
CONTROLS	30	295.27	27.74		

where ** indicates p value is highly significant

TABLE 3 shows the P300 latency values of diabetics and controls. The difference in mean P300 latency values is statistically significant (p value=0.001**).

GRAPH 1: CORRELATION OF P300 LATENCY (ms) WITH DURATION OF DIABETES MELLITUS:



GRAPH 1 shows significant positive correlation(r=0.390*; p=0.033). * Correlation is significant at the 0.05 level.

TABLE 4: ASSOCIATION BETWEEN P300 LATENCY (ms) AND HYPERTENSION IN DIABETICS

Diabetics	Number of subjects	Mean P300 latency(ms)	Std. Deviation	t value	p value
Hypertensives	13	350.32	20.03	3.252	0.003*
NonHypertensives	17	317.15	35.25		

TABLE 4 shows association between P300 latency and hypertension in diabetics. There is significant difference in means of P300 latency between diabetic hypertensives and diabetic nonhypertensives with p value=0.003*.

***** is significant at the 0.05 level.

TABLE 5: ASSOCIATION BETWEEN P300 LATENCY (ms) AND DYSLIPIDEMIA IN DIABETICS

Diabetics	Number of subjects	Mean P300 latency(ms)	Std. Deviation	t value	p value
Dyslipidemia	8	346.61	17.07	2.081	0.047*
No dyslipidemia	22	326.04	36.70		

TABLE 5 shows association between P300 latency and dyslipidemia in diabetics. There is significant difference in means of P300 latency between diabetics with dyslipidemia and diabetics without dyslipidemia with p value=0.047*.

***** is significant at the 0.05 level.

TABLE 6: ASSOCIATION BETWEEN P300 LATENCY (ms) AND SMOKING IN DIABETICS:

Diabetics	Number of subjects	Mean P300 latency(ms)	Std. Deviation	t value	p value
Smokers	12	360.94	16.85	6.120	0.001**
Nonsmokers	18	311.92	26.99		

TABLE 6 shows association between P300 latency and smoking in diabetics. There is significant difference in means of P300 latency between diabetic smokers and diabetic nonsmokers with p=0.001**.

where ** indicates p value is highly significant.

DISCUSSION

DISCUSSION

Diabetes is a chronic disease that leads to chronic long term complications including risk of cognitive changes**.** [67,68,69] Although diabetes is considered to be a risk factor for cognitive impairment, the cognitive function of patients with type 2 diabetes is not usually evaluated in routine clinical care. Besides this, type 2 diabetes and dementia are common in the elderly, which are often progressive and disabling conditions.[67]

Most screening instruments are relatively short and easy to administer and have been developed for a specific population or neurological condition. Ideally, screening instruments have both high sensitivity and specificity, not only maximizing the probability of identifying individuals with cognitive decline, but also minimizing the probability of incorrectly classifying an individual as cognitively impaired. The Mini- Mental State Examination (MMSE) is a screening instrument that has been developed to determine whether older adults have cognitive impairments that are in agreement with the clinical criteria for Alzheimer's dementia.[7]

Among all objective cognitive tests, P300 Event related potential is considered to be a very sensitive tool for studying cognition in diabetes. P300 Event related potential reflects the speed of neural events related to attention and short term memory.[70] Event-related potentials (ERP), in particular the P300 has been used as an electro physiological index of cognitive impairment in recent years.[10] Increase in P300 latency has been associated to abnormalities in psychometric tests in diabetic patients.

MMSE scores was used as a screening tool to assess cognitive function in all subjects. Subjects chosen had MMSE score of more than 25. A score of less than 25 indicates cognitive dysfunction. The MMSE scores between diabetics and controls in our study were comparable showing no signs of cognitive dysfunction.

In the present study, NIDDM patients showed significantly higher latencies of ERP P300 than controls which is in accordance with other studies. [70-76] P300 ERPs were able to reveal cognitive changes not detected by neuro-psychometric test (MMSE). Thus, P300 may be helpful in early detection of cognitive decline in DM and in identifying diabetic patients with potential pre-senile dementia. P300 auditory event-related potentials can be used as a sensitive indicator to assess cognitive impairment for early diagnosis.

The probable cause for prolonged P300 wave could be chronic sustained hyperglycaemia. Hyperglycaemia has potentially toxic effects on neurons in the brain through osmotic insults, oxidative stress mediated free radical formation, increased release of inflammatory cytokines and non enzymatic glycosylation which irreversibly modifies tissue proteins and organ functions. Moreover, chronic hyperglycemia is thought to contribute to reduced hippocampal neurogenesis and consequently hippocampal atrophy and cell death. In support to these observations, in a recent resting-state functional magnetic resonance imaging study, it was provided evidence of reduced functional hippocampal connections bilaterally to widespread regions in T2DM patients compared to healthy controls. Additionally, it has been suggested that connections between the P300 generators, i.e. the white matter volume, have a more profound impact on P300 than the size of the generators themselves.[9]
Since P300 is thought to be produced by interactions between frontal lobe and hippocampal/temporal–parietal processes it could be hypothesized that the prolonged P300 latency in T2DM reported in the present study, might possibly reflect these neuropathological and functional alterations associated with the hippocampal circuitry, which is involved in learning and working memory.

Significant positive correlation was found in the present study between P300 latencies and the duration of DM suggesting that patients with longer duration of diabetes had longer P300 latencies. Electrophysiological P300 test revealed that disease course of diabetic patients are significantly associated with P300 latencies.[70,71] Since P300 latencies represent conduction time in neural circuitry involved in cognitive task,[77] DM hampers the signal conduction in the neural network, which further deteriorates as the duration of disease increases.

These findings suggest that DM duration is important in the pathogenesis of cognitive impairment. It is possible that metabolic imbalances and other factors could interact either directly or indirectly and result in an altered central nervous system function and impaired cognition. Long duration of DM being an atherogenic factor it may increase the risk of cognitive dysfunctioning through well recognized associations with stroke, causing cerebral macrovascular disease and cerebral infarctions. Chronic hyperglycemia is one of the determinants of cognitive decline in people with T2DM. The deleterious effects of hyperglycemia are mediated through an increased influx of glucose through the polyol pathway forming sorbitol and fructose, oxidative stress, and non-enzymatic glycation of biomolecules resulting in advanced glycation end products (AGE).[70]

Other likely mechanisms of cognitive dysfunction in T2DM are extensive leukoaraiosis (White matter hyperintense lesions– WMHLs), atrophy in the region of hippocampus and amygdala and insulin resistance. Insulin resistance contributes through the indirect mechanism of up-regulating hypothalamic–pituitary–adrenal axis, thereby causing hypercortisolemia related cognitive dysfunction.[70]

Few other studies could not find any linear correlation between P300 latencies and the duration of DM.[9,76,78] It is interesting to note that there is greater decline in

global cognitive performance in middle-aged diabetics, as compared to the controls indicating that accelerated brain ageing might be present in T2DM patients. Specifically, it has been suggested that decline in speed of cognitive processes is greater during the early stages of diabetes, whereas affection of memory is unremitting.[9] The decline in speed of cognitive processes is greater during the early stages of diabetes. Hence, the absence of correlation of P300 latencies with disease duration is not surprising.[9]

In our study, significant difference was found in P300 latency between diabetic hypertensives and diabetic nonhypertensives and also between diabetics with dyslipidemia and diabetics without dyslipidemia. Hypertension usually exists as a co-morbid condition with DM and may be a part of a larger metabolic syndrome, including hyperglycemia, hyperinsulinemia, and dyslipidemia. Diabetes usually does not occur isolated. Hypertension and diabetes, when combined, increase the risk of cognitive impairment.[79,80,81]A similar study also revealed a higher association of hypertension with diabetic group than control group, and there was significant difference in P300 trends with co-existence of DM and hypertension than DM alone.[70] Although several mechanisms may interact in order for diabetes and hypertension to cause cognitive impairment, hypertension causes cognitive decline through the vascular consequences of blood pressure load on the cerebral circulation, both on large and small vessels. Large vessel disease mainly occurs through increased atherosclerosis and arterial stiffness, whereas small vessel disease is sustained by vascular remodeling, endothelial dysfunction, and the impairment of cerebral blood flow auto-regulation with increased susceptibility to hypo-perfusion. All these cause discrete brain lesions such as ischemic or hemorrhagic stroke, with the loss of brain tissue and cognitive deterioration.[70]

Cognitive decline with age is well known. In this study, we have recruited age matched controls, thus, negating the influence of age and assessing the impact of DM on cognitive function. Our study proves that diabetes is a risk factor independent of age in the development of cognitive dysfunction.

In the present study, a significant difference in P300 latency was observed between diabetic smokers and diabetic non-smokers. A study showed significantly longer latency in smokers which may explain the direct effect of tobacco smoking and nicotine on the cognitive function, as mentioned in other studies[82,83,84].

Other studies which have differed have used non-technical psychological tests (like intelligence test, memory test...etc).[85,86] which are influenced by increased mental alertness after smoking.

The findings of this study support the hypothesis that there is a relationship between cognitive dysfunction and diabetes mellitus.P300 is a sensitive tool that can be used for detection of early cognitive impairment in diabetics in whom MMSE has failed to detect cognitive impairment. Presence of coexisting conditions like hypertension, dyslipidemia and smoking in diabetics appear to aggravate cognitive impairment in a significant way.

SUMMARY AND CONCLUSION

SUMMARY

This study was conducted in the Department of Physiology, Sri Devaraj Urs Medical College, Kolar, to evaluate the effect of diabetes on cognition using P300 Event Related Potential. 30 diabetics and 30 age and sex matched controls with MMSE scores more than 25 indicating no cognitive impairment were selected for the study and were subjected to pure tone audiometer and ERP P300 recordings. Statistical analysis revealed that diabetics had significantly prolonged P300 wave latencies than that of the controls indicating cognitive decline. Within the study group, P300 latencies positively correlated with duration of diabetes, thus confirming that duration of disease could be associated with decline in cognition. There was significant difference in P300 with co-existence of DM and hypertension than DM alone and also among diabetics with dyslipidemia and diabetics without dyslipidemia. Significant difference in P300 latency was observed between diabetic smokers and diabetic non-smokers. P300 proved to be a reliable index of central nervous system dysfunction in diabetes mellitus and more sensitive than neuropsychologica1 testing (MMSE) and P300 could be used to prospectively evaluate the effects of therapeutic interventions on cognitive function in type 2 diabetes mellitus.

CONCLUSIONS

1. Significantly higher latencies of ERP P300 were found in NIDDM patients than controls. P300 ERPs were able to reveal cognitive changes not detected by neuro-psychometric test (MMSE). Thus, P300 may be helpful in early detection of cognitive decline in DM and in identifying diabetic patients with potential pre-senile dementia.

   P300 auditory event-related potentials can be used as a sensitive indicator to assess cognitive impairment for early diagnosis.
2. Significant positive correlation was found between P300 latencies and the duration of DM suggesting cognitive decline with increase in duration of diabetes.
3. Significant difference was found in P300 latency between diabetic hypertensives and diabetic nonhypertensives and also between diabetics with dyslipidemia and without dyslipidemia suggesting that hypertension, dyslipidemia and diabetes when combined, increase the risk of cognitive impairment.
4. Diabetes is a risk factor independent of age in the development of cognitive dysfunction
5. Significant difference in P300 latency was observed between diabetic smokers and diabetic non-smokers, which may explain the direct effect of tobacco smoking and nicotine on the cognitive function.

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ANNEXURES

ANNEXURE I

1.	NAME	
2.	AGE	
3.	SEX	
4.	DURATION OF DIABETES	
5.	MEDICAL HISTORY OF HYPERTENSION	
6.	DYSLIPIDEMIA	
7.	SMOKING	

ANNEXURE-II

Table 4.2 Mini-mental State Examination

Orientation
1 point for each correct answer
What is the:
- time
- date
- day
- month
- year — **5 points**

What is the name of this:
- ward
- hospital
- district
- town
- country — **5 points**

Registration
Name three objects
1, 2, 3 points according to how many are repeated
Resubmit list until patient word perfect in order to use this for a later test of recall
Score only first attempt — **3 points**

Attention and calculation
Have the patient subtract 7 from 100 and then from the result a total of five times; 1 point for each correct subtraction — **5 points**

Recall
Ask for three objects used in the registration test, 1 point being awarded for each correct answer — **3 points**

Language
1 point each for two objects correctly named (pencil and watch) — **2 points**
1 point for correct repetition of 'No ifs, ands and buts' — **1 point**
3 points if three-stage commands correctly obeyed: 'Take this piece of paper in your right hand, fold it in half and place it on the floor' — **3 points**
1 point for correct response to a written command, such as 'close your eyes' — **1 point**
Have the patient write a sentence. Award 1 point if the sentence is meaningful, has a verb and a subject — **1 point**
Test the patient's ability to copy a complex diagram of two intersecting pentagons — **1 point**

Total score 30

MASTER CHART (DIABETICS)

SL. NO.	AGE(yrs)	GENDER	P300 LATENCY(ms)	MMSE SCORE	DURATION OF DM(yrs)	HYPERTENSIVE	DYSLIPIDAEMIA	SMOKING
1.	61	M	333.3	25	15	yes	yes	yes
2.	60	M	337.5	25	10	yes	yes	yes
3.	71	M	381.3	25	17	yes	no	yes
4.	67	M	372.9	25	6	no	no	yes
5.	69	M	366.7	26	5	no	no	yes
6.	60	M	372.9	26	8	no	no	yes
7.	65	M	360.4	29	7	no	no	yes
8.	70	M	340.6	27	6	yes	yes	no
9.	69	M	347.9	27	6	no	no	yes
10.	60	M	280.2	28	2	no	no	no
11.	71	M	342.7	25	9	yes	yes	no
12.	72	M	379.2	25	11	yes	no	yes
13.	75	M	289.6	28	3	no	no	no
14.	70	M	379.2	25	8	yes	yes	yes
15.	61	M	320.8	25	6	yes	no	no
16.	58	M	295.8	28	20	no	no	no
17.	73	M	281.3	28	4	no	no	no
18.	63	M	344.8	25	8	yes	yes	no
19.	60	M	318.8	25	5	no	no	no
20.	55	M	349	25	7	yes	no	yes
21.	59	M	333.3	27	8	no	no	no
22.	73	M	286.5	28	3	no	no	no
23.	55	F	365.6	26	10	yes	yes	no
24.	50	F	320.8	26	8	no	no	no
25.	60	F	270.8	28	3	no	no	no
26.	50	F	329.2	25	6	yes	yes	no
27.	45	F	303.1	25	3	no	no	no
28.	61	F	299	29	9	no	no	no
29.	50	F	291.7	28	3	no	no	no
30.	55	F	351	25	7	yes	no	yes

MASTER CHART (CONTROLS):

SL. NO.	AGE(yrs)	GENDER	P300 LATENCY(ms)	MMSE SCORE	HYPERTENSIVE	DYSLIPIDAEMIA	SMOKING
1.	61	M	283.3	26	yes	yes	yes
2.	72	M	347.9	27	no	no	no
3.	60	M	250	26	no	no	no
4.	75	M	259.4	27	yes	no	no
5.	59	M	279.2	25	no	no	no
6.	55	M	252.1	28	yes	yes	yes
7.	59	M	302.1	25	yes	yes	no
8.	73	M	308.3	25	no	no	no
9.	75	M	302.1	25	no	no	no
10.	61	M	284.4	28	no	no	no
11.	61	M	267.7	28	yes	no	no
12.	65	M	306.3	25	no	yes	yes
13.	67	M	313.5	25	no	no	no
14.	69	M	264.6	28	no	no	no
15.	70	M	301	25	no	no	no
16.	69	M	277.1	28	yes	yes	no
17.	72	M	332.3	25	no	no	no
18.	55	M	315.6	25	no	no	no
19.	60	M	254.2	26	no	no	no
20.	71	M	345.8	25	no	no	no
21.	59	M	303.1	26	no	no	no
22.	61	M	305.2	26	no	no	no
23.	50	F	293.8	28	yes	yes	yes
24.	73	F	317.7	26	no	no	no
25.	61	F	333.3	25	yes	no	no
26.	60	F	269.8	27	no	no	no
27.	55	F	263.5	28	no	no	no
28.	55	F	315.6	26	no	no	no
29.	45	F	286.5	28	no	no	no
30.	50	F	322.9	26	yes	yes	no