ORIGINAL ARTICLE

Brain Wave Changes during Cognitive Task Performance in Uncomplicated Diabetic Adults: An Exploratory Study

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is a chronic disease associated with cognitive decline and dementia in the elderly population. This exploratory study analysed the brain wave changes during cognitive task performance in working adults with and without type 2 diabetes mellitus (T2DM). **MATERIALS AND METHODS:** The Mini-Mental State Examination was used to screen subject's cognitive function and quantitative electroencephalography was used to analyse subject's brain waves at rest and whilst performing the serial seven test. **RESULTS:** When performing the serial seven test, the diabetic group showed a higher absolute power of theta waves in the left frontal (Fp1, 16.22 ± 3.81 vs 3.75 ± 1.69; p = 0.022) and temporal regions (T3, 24.27 ± 3.69 vs 7.92 ± 2.17; p = 0.045), but lower absolute power of beta waves in both the frontal regions (Fp1, 27.35 ± 3.67 vs 41.14 ± 5.67; p = 0.029; Fp2, 23.01 ± 3.31 vs 39.05 ± 2.64; p = 0.041) and left temporal region (T3, 37.93 ± 4.64 vs 50.94 ± 3.56; p = 0.046) when compared to those of the control group. The diabetic group took longer to complete the task (127.9 ± 8.3 s vs 95.6 ± 5.9 s; p = 0.032) than the control group, despite no statistically significant difference in correct response rates. Diabetes duration was positively correlated with the theta/alpha ratio in the left frontal (Fp1, r = 0.525; p = 0.041) and temporal (T3, r = 0.618; p = 0.037) regions. **CONCLUSIONS:** T2DM may affect cognitive function in patients before clinical manifestation.

Keywords
Cognitive function, diabetes mellitus, quantitative electroencephalogram

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease and global public health concern. There are approximately 422 million diabetics worldwide, and the prevalence of diabetes in low-and middle-income countries has rapidly increased over the past three decades.[1] Type 2 diabetes mellitus (T2DM) is the most common presenting form in adults, with associated insulin resistance leading to hyperglycaemia.[2] Physical inactivity, tobacco use, high dietary intake of sugar and saturated fat, and obesity have been recognised as the major risk factors associated with T2DM.[3]

Diabetes-associated complications can affect almost all body systems, especially in patients with uncontrolled glycaemia. Destructive macrovascular (cardiovascular, cerebrovascular, and peripheral artery diseases) and microvascular complications (nephropathy, retinopathy, and neuropathy) lead to increased mortality, kidney impairment, blindness, limb amputation, and an overall decreased quality of life.[4,5] Other diabetic complications include increased risk of infection and birth complications. [6,7]

According to the National Diabetes Registry, 902,991 diabetic patients received treatment at primary care facilities governed by the Malaysian Ministry of Health in 2020, and 99.33% of these patients were diagnosed with T2DM.[8] The majority (33.75%) of T2DM patients were aged between 50–59 years, and approximately 14.38% were diagnosed with nephropathy, 11.52% with retinopathy, and 5.64% with ischaemic heart disease.

In addition to the above-mentioned complications, studies have shown that DM increases the risk of cognitive impairment and dementia.[9,10] It has further been reported that the decline of global cognitive function is almost

2–2.5 times greater in middle-aged and older diabetic patients compared to those without diabetes over a 5-year period.[11,12] Further, similar deficits in global cognitive function, executive function, and processing speed have been reported with pre-diabetes.[13]

Quantitative electroencephalogram (QEEG) is a tool used to measure the brain electrical activities in the form of brain waves. It has been used to study the brain waves in patients with mild cognitive impairment, dementia and Alzheimer disease.[14,15] Studies revealed the decreased of high frequency (Delta, 1-4 Hz, and Theta, 4-8 Hz) and increased in low frequency (Alpha, 8-12 Hz, and Beta, 12-35 Hz) brain waves among patients with cognitive impairment in different brain areas.[14,15] These changes were believed to be the damage in cortical cells and desynchronization of the brain electrical activities.

Currently, there are no definitive pharmacological agents that can reverse or improve the symptoms of dementia effectively. Therefore, it is important to detect early cognitive impairment in patients with diabetes and to monitor their disease progression. In this study, we aimed to compare the brain waves of uncomplicated diabetic and healthy participants whilst performing cognitive tasks using QEEG.

MATERIALS AND METHODS

Study Design

This exploratory study was approved by the Universiti Malaysia Sarawak, Faculty of Medicine and Health Sciences Research Ethics Committee [UNIMAS/NC-21.02/03-02 Jld.4 (52)]. Data collection took place at the Neurosurgery and Neuro Wellness Clinic, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak from March 2021 until July 2021.

Participants

A total of 46 participants (T2DM, 25; healthy adults, 25) were recruited through convenience sampling (voluntary) among university staff. A questionnaire was used to collect demographic data and health information (body mass index, disease duration, and type of medication).

Inclusion criteria

Volunteers that met the following criteria were included in the T2DM group:

1. Diagnosed with type 2 DM for at least 3 years
2. Controlled diabetic under regular clinic follow-up
3. At least 11 years of formal education

Exclusion criteria

Volunteers that had the following criteria were excluded from the study:

1. Diabetic with neurovascular complications
2. Known cases of congenital central nervous system abnormalities, psychiatric disorders, or systemic autoimmune diseases
3. Previous history of head trauma or central nervous system infection
4. Treatment with antiepileptic, antidepressant, antipsychotic medications, or any medications that cause drowsiness
5. Alcohol consumer

Procedures

The QEEG assessment followed a modified version of the procedure described by Hashim et al.[16] In this study, the serial seven test was used instead of the trail-making test to minimise body movement during QEEG recording. Written consent was obtained before the test from all volunteers who fulfilled the inclusion and exclusion criteria. The Mini-Mental State Examination (MMSE) was used to screen for cognitive impairment by evaluating orientation, recall, attention and calculation, language, visuospatial and command-following abilities; a score of 24 or above was considered normal cognitive function.[17] Participants from both groups underwent brain wave recording using the 8-channel QEEG system (Neuron-Spectrum 1P QEEG System, Neurosoft, Ivanovo, Russia). After applying a skin preparation gel (Nuprep Gel, Weaver, CO, USA), the electrodes (silver/silver chloride) filled with conductive paste (Ten20, Weaver, CO, USA) were positioned at eight sites on the scalp (Fp1, Fp2, T3, T4, C3, C4, O1, and O2) according to the international

10/20 system. The ground electrode was placed on Fpz, in between Fp1 and Fp2. The left and right mastoids served as reference points for all electrodes. All participants were instructed to wash their hair, to not use hair cream on the day of the test, and to ensure adequate rest the night before (minimum 6 hours of sleep). In addition, the participants were instructed to avoid caffeine 24 h before the test. The QEEG recording was performed in a quiet and relaxed environment with the participants seated in a comfortable chair. The room temperature was maintained at 24 ± 2 °C throughout the recording period.

There were two components in the recording, namely rest and task-performance. During rest, participants were instructed to stare directly at a black spot on a white board placed approximately 60 cm in front of them for 3 min (eyes open). They were then instructed to close their eyes (but avoid sleeping) for 3 min. In the task-performing session, the participants were asked to perform the serial sevens test. Whilst writing down the answer on paper, starting at 100, participants continue to deduct 7 until they reach 2 (example, start with mental calculation 100 – 7, write down the answer which is 93, then mental calculation 93 – 7, write down the number, etc.). The participants were reminded to minimise their body movements while performing this task.

Data were recorded using a band-pass filter 0.1 -– 50 Hz and digitised at a sampling rate of 250 Hz. Electroencephalography (EEG) epochs with ocular, muscular, and other types of artefacts were discarded. The absolute power (square microvolt, μV2) of the four main bands, namely delta (0.1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), and beta (13 – 30 Hz), as well as the theta/alpha ratio were automatically generated using digital neurophysiological system software version 2.0.22.1 (Neuron-Spectrum, Neurosoft, Ivanovo, Russia).

Statistical Analysis

The collected data were analysed using SPSS statistical software for windows (v 22.0 ; IBM, Armonk, NY, USA). Quantitative data were presented as mean ± standard deviation. An independent t-test was used to compare the means of the absolute powers of the different brain waves between the diabetic and healthy control groups. The Pearson correlation coefficient was used to measure the correlation between quantitative variables. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1 presents the demographic characteristics of the participants in this study. There were 17 men and 8 women in the diabetic group. Only 2 of the participants in the diabetic group were taking insulin injections, whereas the rest were on oral hypoglycaemic agents. None of the patients were diagnosed with any diabetic micro- or macrovascular complications. All of the diabetic participants scored >24 on the MMSE (mean score, 27.2 ± 1.4).

Table 1: Demographic Characteristics of Participants

	Diabetic (n = 25) Mean (SD)	**Control (n = 25)** Mean (SD)	***t*-Test *p*-Value**
Age (years)	42.5 ± 7.2	39.5 ± 5.71	0.104
BMI (kg/m²)	31.7 ± 5.3	26.2 ± 3.9	**0.047***
Years of education	13.7 ± 1.7	14.6 ± 2.9	0.250
Years of diabetes	9.7 ± 3.6 years (Range 3 – 15)	-	-
MMSE scores	27.2 ± 1.4	28.9 ± 0.8	0.145

*BMI, body mass index; MMSE, Mini-Mental State Examination; SD, standard deviation; *Statistically significant*

The matched control group consisted of 25 volunteers (17 men and 8 women; mean age, 39.5 ± 5.7 years; range, 32 – 49 years). There were no significant age differences between the diabetic and control groups. A statistically significant higher body mass index was observed in the diabetic group compared to that of the control group (31.7 ± 5.3 vs 26.2 ± 3.9, p = 0.047). MMSE scores were lower in the diabetic participants than in the control participants, but these differences were not significant. All the participants were right-handed.

For spectrum analysis of the brain waves, no significant differences were detected in the absolute power for all frequency bands (alpha, beta, delta, and theta) between the diabetic and control groups in all examined brain regions (frontal, temporal, central, and occipital) for resting with both open and closed eyes. However, during the task performance session (Table 2), there was significantly

Table 2: Absolute power of different brain waves between study groups during task performing

Region	Group	Alpha		Beta		Theta		Delta		Theta/Alpha Ratio	
		μV^2 Mean (SD)	*p*-value	μV^2 Mean (SD)	*p*-value	μV^2 Mean (SD)	*p*-value	(μV^2) Mean (SD)	*p*-value	Mean (SD)	*p*-value
Frontal Fp1	DM	5.75 (0.51)	0.183	27.35 (3.67)	**0.029***	16.22 (3.81)	**0.022***	1.78 (0.61)	0.090	2.49 (0.71)	**0.014***
	C	4.53 (1.02)		41.14 (5.67)		3.75 (1.69)		1.36 (0.54)		0.46 (0.24)	
Frontal Fp2	DM	6.53 (0.87)	0.171	23.01 (3.31)	**0.041***	2.72 (0.56)	0.211	1.51 (0.47)	0.063	0.41 (0.12)	0.077
	C	7.51 (2.59)		39.05 (2.64)		2.13 (0.67)		0.93 (0.81)		0.33 (0.09)	
Temporal T3	DM	13.71 (4.21)	0.082	37.93 (4.64)	**0.046***	24.27 (3.69)	**0.035***	3.43 (1.46)	0.055	1.42 (0.46)	**0.048***
	C	11.17 (2.46)		50.94 (3.56)		7.92 (2.17)		2.97 (0.75)		0.63 (0.27)	
Temporal T4	DM	17.22 (4.49)	0.087	19.14 (3.67)	0.070	6.13 (0.42)	0.094	1.33 (0.55)	0.072	0.29 (0.12)	0.082
	C	13.92 (3.89)		21.37 (5.67)		4.99 (1.31)		1.09 (0.77)		0.37 (0.21)	
Central C3	DM	5.27 (0.88)	0.189	13.77 (3.92)	0.064	5.33 (0.67)	0.115	1.47 (0.49)	0.061	1.17 (0.35)	0.077
	C	3.63 (0.55)		17.32 (4.73)		4.21 (0.45)		1.03 (0.67)		1.31 (0.26)	
Central C4	DM	4.41 (0.77)	0.325	14.96 (2.92)	0.076	1.87 (0.87)	0.098	1.33 (0.67)	0.075	0.51 (0.14)	0.065
	C	4.67 (0.92)		13.33 (3.73)		1.44 (0.48)		1.51 (0.79)		0.42 (0.03)	
Occipital O1	DM	3.12 (0.73)	0.186	22.21 (3.78)	0.062	3.75 (0.77)	0.134	1.67 (0.61)	0.068	1.18 (0.31)	0.059
	C	3.70 (0.65)		25.74 (5.37)		3.12 (0.47)		1.35 (0.71)		0.98 (0.15)	
Occipital O2	DM	2.82 (0.67)	0.173	19.12 (3.78)	0.066	4.01 (1.02)	0.137	1.47 (0.82)	0.061	1.38 (0.43)	0.101
	C	3.55 (0.59)		23.42 (2.27)		3.89 (0.31)		1.29 (0.54)		1.21 (0.47)	

*DM, diabetes mellitus; C, control; µV2, square microvolt; SD, standard deviation; *statistically significant*

lower absolute power of beta waves seen in both frontal regions (Fp1, 27.35 ± 3.67 vs 41.14 ± 5.67; p = 0.029; Fp2, 23.01 ± 3.31 vs 39.05 ± 2.64; p = 0.041) and left temporal region (T3, 37.93 ± 4.64 vs 50.94 ± 3.56; p = 0.046) among the diabetic participants compared to that of the control group. The diabetic group showed significantly higher absolute power of theta wave and theta/alpha ratio in the left frontal region (FP1, 16.22 ± 3.81 vs 3.75 ± 1.69; p = 0.022; and 2.49 ± 0.71 vs 0.46 ± 0.24; p = 0.014, respectively) and left temporal region (T3, 24.27 ± 3.69 vs 7.92 ± 2.17; p = 0.035; and 1.42 ± 0.46 vs 0.68 ± 0.27; p = 0.048, respectively) compared to that of the control group. No other significant differences in absolute power of the other frequency bands were observed.

During task performance, the diabetic group took a significantly longer time to complete the serial sevens test compared to that of the control group (127.9 ± 8.3 s vs 95.6 ± 5.9 s; p = 0.032; Table 3). Although the number of correct responses was higher in the control group, this difference was not statistically significant.

In addition, the theta/alpha ratio was positively correlated with diabetes duration in the left frontal (FP1, r = 0.485, p = 0.041) and left temporal (T3, r = 0.518, p = 0.037) regions (Table 4). No significant correlation was observed between the theta/alpha ratio in these two regions, and the body mass index and MMSE scores among patients with diabetes.

Table 3: Duration and Scores for Task Performing

	Diabetic (n = 25) Mean (SD)	**Control (n = 25)** Mean (SD)	***t*-Test *p*-Value**
Correct Response (%)	77.62 (11.9)	84.25 (13.7)	0
Response Time (s)	127.9 (8.3)	95.6 (5.9)	**0.032***

*s, seconds; SD, Standard Deviation; *Statistically significant*

Table 4: Correlation between Theta/Alpha ratio and duration of diabetes

	Theta / alpha ratio			
	Brain Regions			
	Left Frontal (Fp1)		**Left Temporal (T3)**	
	Correlation coefficient (*r*)	*p*-value	Correlation coefficient (*r*)	*p*-value
Duration of DM	r = 0.525	0.041*	r = 0.618	0.037*

*DM, Diabetes Mellitus; *Statistically significant*

DISCUSSION

According to the National Health and Morbidity Survey 2019, there are approximately 3.9 million Malaysian adults (1:5) living with diabetes.[18] The prevalence of diabetes has increased from 11.2% in 2011 to 18.3% in 2019. From the same survey, it was noted that 8.5% of adults in the 30 – 39 age group and 12.4% in the 40 – 49 age group were unaware of their condition. In fact, Malaysia has the highest ratio of diabetes prevalence to total adult population in Western Pacific region.[19] Diabetes is one of the three major preventable health conditions included under the National Strategic Plan for the Non-Communicable Disease 2016–2025.[20] Furthermore, the total cost of diabetes management in Malaysia was estimated to be around USD 600 million per year.[21]

The macrovascular and microvascular complications of diabetes have been well documented.[2,22] And now, diabetic patients have been associated with reduced performance in numerous cognitive function domains,[23] and reported to have a 1.5 – 2 times higher risk of developing dementia.[24] In addition, both diabetes and pre-diabetes status have also been found to accelerate the rate of progression from mild cognitive impairment to dementia.[25] The exact pathophysiology of cognitive dysfunction in diabetic patients remains unclear. Several hypotheses[26-30] have attributed the diabetes-associated cognitive impairment to i) hyperglycaemia-induced neurotoxicity; ii) diabetic vasculopathy; iii) oxidative damage on neuronal cells, and iv) disruption of the normal cortical ability in utilising insulin.

QEEG is a neurophysiological tool used to detect electrical activity in the brain that has been applied in the study of diabetic patients to examine the changes in their brain waves. Study by Panta et al. demonstrated an increase in low-frequency slow waves (delta and theta) in different sites of the brain in participants with T2DM (mean age, 52.87 ± 2.6) that was suggestive of diffuse central neuropathy.[31] A decrease in alpha wave activity in the left parietal region among elderly with T2DM (mean age, 62.6 ± 4.3) was seen in a study by Bethiun and Premaraja.[32] However, an inconsistency between these two studies was that the Beta wave activity was increased in the first, and decreased in the second.[31,32] Abo Hagar et al. further divided the alpha waves into alpha 1 (low Alpha, 8 ≤ 11 Hz) and alpha 2 (high alpha, 11 ≤ 14 Hz), and demonstrated a decrease in alpha 1 activity and an increase in alpha 2 activity in elderly with T2DM with mild cognitive impairment (mean age, 63.75 ± 6.83); the alpha 2/alpha 1 ratio was found to be associated with hippocampal atrophy.[33] In another study by Bian et al., a higher theta/alpha ratio was observed in patients with T2DM (mean age, 69.7 ± 8.4) with amnestic mild cognitive impairment (aMCI) compared to non-aMCI diabetic patients.[34] An increase in theta power in the frontal, temporal, and occipital regions is associated with cognitive decline and lack of attention.[14,15] In these previous studies, they were looking at the brain waves of diabetic patients mainly in the resting condition. Most of these studies involved elderly subjects and some of them presented with mild cognitive impairment. In addition, these studies did not state the duration of diabetes or mention if their subjects had developed other diabetic complications while the brain waves were recorded. In our current study, we recruited middle-aged diabetic patients with no documented diabetic complications. And we looked at the brain waves of the subjects both in resting condition as well as when they were performing a cognitive task. In contra with the previous studies, we did not see any significant difference in the brain waves pattern between the diabetic and healthy subjects when they were in resting condition. Thus, this study did not show any evidence of diffuse central neuropathy among the diabetic patients in resting state as found by Panta et al.[31] This could be due to the difference in the age group of subjects, where our subjects are younger compared to the previous studies.

In addition to the resting state, we have also explored the brain wave changes in diabetic participants while they were performing a cognitive task. These diabetic participants did not have any documented diabetic complications and scored more than 24 points on MMSE screening. The serial seven test (also known as serial subtraction by seven) is a quick test to assess mental function, especially in the domains of attention and mental concentration.[36] It is interesting to see the changes in the brain waves in certain brain regions while performing this cognitive task, although there was no significant difference in the mean scores of MMSE screening and in the percentage of correct responses in the serial seven test between the diabetic and control groups. We observed an increase in the low frequency wave (theta) and a decrease in high frequency wave (beta) mainly at bilateral frontal and left temporal regions. These findings suggested diabetic patients might have some difficulties in attention while performing mental calculation despite they have no clinical presentation.

Commonly reported cognitive abnormalities in diabetic patients are learning and memory deficits.[37] Insulin receptors are found on neurones in brain areas related to learning and memory, such as the hippocampus and parts of the cerebral cortex.[38] Thus, it is possible that insulin disorders may affect glucose metabolism in these areas.

And both long duration of diabetes and chronic hyperglycaemia have been associated with an increased risk of cognitive dysfunction.[39] Other affected cognitive domains reported in diabetic patients include attention, executive function, information processing, psychomotor efficiency, and verbal fluency.[40]

The frontal lobe is related to many functions, including executive function, attention, memory, speech, behaviour, and emotion control.[41,42] In addition, the frontal lobe is connected to other subcortical areas such as the basal ganglia and thalamus to form the frontal subcortical circuits.[42] Meanwhile, the left temporal lobe is related to language comprehension, speech formation, learning, memory processing, and facial recognition.[43] The left side is the dominant temporal lobe in most people. [43]

During task performance (serial seven test), the absolute power of the beta waves in the bilateral frontal and left temporal regions was significantly lower in the diabetic group than in the control group. Beta waves are high-frequency brain waves that oscillate between 12–35 Hz, and are commonly observed during eye-open arousal, deep thought, and focused attention.[32] Thus, when someone is performing cognitive tasks, increased beta waves in the frontal regions are expected. Whereas, the theta waves are low-frequency brain waves that oscillate between 4–8 Hz, and are commonly observed in drowsiness, dreamlike, distracted, or unfocused states.[31] And these low-frequency waves are usually very minimal or absent when a person is in an awake condition. Increases in theta waves have been associated with neurodegeneration in the elderly, as well as mild cognitive impairment and Alzheimer's disease patients.[15] In our study, the absolute power of the theta waves in the left frontal and left temporal regions was significantly higher in the diabetic group than in the control group during task performance (serial seven test). These unusual beta and theta activities found in diabetic subjects while performing mental calculations might be related to the effect of hyperglycaemia and insulin insensitivity on certain brain regions namely the frontal cerebral cortex and the hippocampus in the deep temporal region as insulin receptors are present in these areas.[40]

Abnormal increases in the theta/alpha ratio have been associated with cognitive deficits in the elderly and diabetic patients with amnesia.[43] In our study, none of the diabetic participants complained of any cognitive problems; however, the presence of significantly higher theta activity and theta/alpha ratios over the left frontal and left temporal lobes during mental calculation was unusual. The diabetic participants took significantly longer duration to complete the cognitive task, although there was no significant difference in the correct response rate compared to the control group. The increased theta/alpha ratio in diabetic participants suggests that diabetes might have affected their cognitive speed, despite no clinical manifestation of cognitive impairment. However, we did not find any correlation between the MMSE scores and the theta/alpha ratio. This is probably the insulin insensitivity and the degree of neuronal damage vary among the diabetic patients.

Study limitations

The sample size in this study was small, and the participants were recruited through convenience sampling from a single university. Thus, the results may not be a true representation of all middle-aged patients with diabetes. Data collection was affected by the COVID-19 pandemic, and it only took place during the recovery phase of the movement control order (MCO) within a limited timeframe. The pandemic discouraged participation. The study did not include biochemical data such as fasting blood sugar, haemoglobin A1c (HbA1c), and renal profile, because the majority of participants were not able to attend the follow-up appointment during the MCO for blood tests. Thus, diabetic control information was based on the past medical records and personal disclosure of participants. The abstained of coffee and other stimulants before the study of brain waves was based on self-reporting.

CONCLUSION

The changes in brain waves observed in diabetic patients during cognitive task performance suggest that diabetes may affect cognitive function before the clinical manifestation of cognitive changes or other complications.

Public awareness and education on diabetes prevention should be re-emphasised regularly since there is currently no definite treatment to improve cognitive decline or dementia symptoms. Understanding and preventing diabetes associated cognitive deficits remain key priorities for future research.

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CONFLICTS OF INTERESTS

We declare no conflict of interests.

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