

Investigating Cognitive Function in Clinical and Non-clinical Samples using Electroencephalography and Psychometric Assessment: A Comparative Study

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I. Declaration

I, George Kalatzis, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy (Science), in the School of Life Sciences at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Production Note:

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II. Acknowledgements

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III. Thesis Format

This thesis is formatted as a conventional thesis and hence is structured as a series of chapters.

IV. Publications and Presentations

Published Abstracts/Conference Presentations:

1. Lees, T., Maharaj, S., **Kalatzis, G.**, Nassif, N., Newton, P., & Lal, S. The neurocognitive relationship between stress and anxiety, memory and decision-making performance of Australian Nurses. Poster presentation: 58th Annual meeting of the Society for Psychophysiological Research 2018, Quebec City, Canada.
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4. **Kalatzis, G.**, Lees, T., Nassif, N., Zaslowski, C., & Lal, S. Investigating cognitive function in diseased states: electroencephalography (EEG) and psychometric assessment. Poster presentation: The New Horizons Conference 2015, Sydney, 23rd – 25th November.
5. Lees, T., **Kalatzis, G.**, & Lal, S. (2015). Examining negative mental states and their association to psychometric and electroencephalographic measures of cognitive performance in Australian Nurses. *Psychophysiology*, 52 (S24), doi: 10.1111/psyp.12495.
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Other (manuscripts currently submitted or pending outcome):

1. Lees, T., Maharaj, S., **Kalatzis, G.**, Nassif, N., Newton, P., & Lal, S. (2020). Electroencephalographic prediction of global and domain-specific cognitive performance of clinically-active Australian Nurses. *Physiological Measurement* (Accepted – 20/08/2020).
2. **Kalatzis, G.**, Lees, T., Nassif, N., Zaslowski, C., & Lal, S. (2020). Changes in EEG activity as an indicator of early cognitive dysfunction in diabetes mellitus: a review. *Journal of Diabetes and Its Complications* (Due for resubmission).

V. Table of Contents

I. Declaration	ii
II. Acknowledgements.....	iii
III. Thesis Format	v
IV. Publications and Presentations	vi
V. Table of Contents.....	viii
VI. List of Figures	xiii
VII. List of Tables	xviii
VIII. Abbreviations.....	xxiii
IX. Abstract	xxvii
Chapter 1 – Introduction	1
1.1 Ageing and Health.....	1
1.2 Cognition.....	4
1.2.1 Mild Cognitive Impairment (MCI).....	7
1.2.2 Major Neurocognitive Disorder (NCD) (Dementia)	11
1.2.3 Alzheimer’s Disease (AD).....	15
1.2.4 Vascular Dementia (VaD)	21
1.3 Risk Factors for Cognitive Impairment.....	22
1.3.1 Diabetes Mellitus	24
1.3.2 Type 1 Diabetes Mellitus (T1DM)	26
1.3.3 Type 2 Diabetes Mellitus (T2DM)	27
1.4 Diabetes mellitus: Complications	32
1.5 Diabetes Mellitus and Cognitive Function.....	34
1.5.1 Type 1 Diabetes Mellitus (T1DM) and Cognitive Function	37
1.5.2 Type 2 Diabetes Mellitus (T2DM) and Cognitive Function	40
1.6 Mechanistic Contributors to Cognitive Dysfunction in Diabetes	41
1.6.1 Hyperglycaemia.....	41
1.6.2 Recurrent Hypoglycaemia	43
1.6.3. Altered Insulin Signalling.....	45
1.6.4. Blood-brain Barrier Dysfunction.....	48
1.7 High Blood Pressure	51
1.7.1 Hypertension: Complications	53

1.7.2 Hypertension and Cognitive Function	55
1.7.3 High Blood Pressure and Cognition: Evidence from Cross-sectional Studies	56
1.7.4 High Blood Pressure and Cognition: Evidence from Longitudinal Studies	57
1.8 Mechanistic Contributors to Cognitive Dysfunction in Hypertension.....	59
1.8.1 Blood-brain Barrier Dysfunction.....	59
1.8.2 Impaired Neurovascular Coupling.....	60
1.8.3 Small Vessel Disease (SVD)	62
1.9 Electroencephalography (EEG)	64
1.9.1 Delta Waves.....	67
1.9.2 Theta Waves	67
1.9.3 Alpha Waves.....	67
1.9.4 Beta Waves	67
1.9.5 Gamma Waves.....	68
1.10 Electroencephalography Changes in Diabetes Mellitus.....	69
1.10.1 Changes in Slow-wave EEG activity in Diabetes Mellitus	70
1.10.2 Changes in Fast-wave EEG activity in Diabetes Mellitus.....	72
1.11 Electroencephalography Changes in Hypertension	78
1.12 Effect of glucose lowering and anti-hypertensive medication on EEG.....	80
1.13 Basis and Study Significance.....	81
1.13.1 Implications of the Present Study	81
1.14 Hypotheses.....	84
1.15 General Aims	84
1.16 Specific Aims (Aim 1).....	85
1.17 Specific Aims (Aim 2).....	85
Chapter 2 – Methodology.....	86
2.1 Methodology Summary	86
2.2 Ethics Approval and Consent	86
2.3 Recruitment of Study Participants.....	87
2.4 Study Inclusion/Exclusion Criteria.....	87
2.5 Blood Pressure Measurement	88
2.5.1 BP Inclusion/Exclusion Criteria	90
2.6 Blood Glucose Level (BGL) Determination	93

2.7 Demographic Data Acquisition	95
2.7.1 Lifestyle Appraisal Questionnaire (LAQ)	95
2.8 Electroencephalography Data Acquisition	97
2.8.1 Stroop Colour Word Test	101
2.9 Cognitive Assessment.....	102
2.9.1 Mini-Mental State Examination (MMSE).....	103
2.9.2 Cognistat.....	106
2.10 Data Processing and Analysis.....	113
2.10.1 Electroencephalography Data Pre-Processing	113
2.11. Statistical Analysis	115
2.11.1 Power Analysis	115
2.11.2 Dependent Sample T-test.....	115
2.11.3 Wilcoxon Signed Rank Test	115
2.11.4 Mann Whitney U Test.....	116
2.11.5 Partial Pearson’s Correlation	116
2.11.6 Spearman’s Rank Order Correlation.....	116
2.11.7 Multiple Analysis of Covariance (MANCOVA).....	117
Chapter 3 – Results: Demographic Characteristics (Non-clinical and clinical)	118
3.1 Participant Summary	119
3.2 Demographic Variables	119
3.2.1 Cardiovascular Variables (SBP, DBP, and HR).....	122
3.2.2 Blood Glucose Level (BGL).....	125
3.2.3 Disease-specific Variables.....	127
Chapter 4 – Associations between Blood Pressure, Blood Glucose Level, and Cognitive Performance (Non-clinical).....	129
4.1 Cognitive Performance	129
4.1.1 Global Cognitive Performance (MMSE).....	129
4.1.2 Domain-specific Cognitive Performance	130
4.1.3 Stroop Colour Word Test.....	133
4.2 Associations between BP and Cognition for the Non-clinical Group	137
4.3 Associations between BGL and Cognition for the Non-clinical Group	137
4.4 Associations between BP, BGL, and Cognition for the T1DM Group	139
4.5 Associations between BP, BGL, and Cognition for the T2DM Group	141
4.6 Associations between BP, BGL, and Cognition for the HTN Group.....	145

4.7 Discussion: Cognitive Performance of Non-clinical and Clinical Groups.....	147
4.7.1 Cognitive Performance: Clinical Groups (T1DM, T2DM, and HTN).....	147
4.8 Associations: Non-clinical Group.....	155
4.9 Associations: Clinical Groups	157
4.10 Conclusions: Cognitive Performance	159
Chapter 5 – Associations between Blood Pressure, Blood Glucose Level, and Electroencephalography (Non-clinical).....	160
5.1. Associations between pre-study SBP and EEG activity.....	160
5.2 Associations between post-study SBP and EEG activity	168
5.3 Associations between pre-study DBP and EEG activity	171
5.4 Associations between post-study DBP and EEG activity.....	173
5.5 Associations between pre-study BGL and EEG activity.....	176
5.6 Associations between post-study BGL and EEG activity	180
5.7 Discussion: Associations between BP and BGL and EEG.....	182
5.7.1 Associations between BP and EEG	182
5.7.2 Associations between BGL and EEG	185
5.8 Conclusions.....	189
Chapter 6 – Associations between Blood Pressure, Blood Glucose Level, and Electroencephalography (Clinical)	190
6.1 Type 1 Diabetes Mellitus.....	190
6.1.1 Associations between pre-study SBP and EEG activity.....	190
6.1.2 Associations between pre-study DBP and EEG activity	195
6.1.3 Associations between pre-study BGL and EEG activity.....	197
6.1.4 Associations between post-study SBP and EEG activity	202
6.1.5 Associations between post-study DBP and EEG activity	203
6.1.6 Associations between post-study BGL and EEG activity	206
6.1.7 Associations between disease-specific variables and EEG activity	211
6.2 Type 2 Diabetes Mellitus.....	214
6.2.1 Associations between pre-study SBP and EEG activity.....	214
6.2.2 Associations between post-study SBP and EEG activity	218
6.2.3 Associations between DBP (pre and post) and EEG activity.....	221
6.2.4 Associations between BGL (pre and post) and EEG activity.....	221
6.2.5 Associations between HbA _{1c} and EEG activity	224
6.2.6 Associations between disease duration and EEG activity.....	226

6.3 Hypertension.....	229
6.3.1 Associations between pre-study SBP and EEG activity.....	229
6.3.2 Associations between post-study SBP and EEG activity	231
6.3.3 Associations between pre-study DBP and EEG activity	233
6.3.4 Associations between post-study DBP and EEG activity	236
6.3.5 Associations between pre-study BGL and EEG activity.....	239
6.3.6 Associations between post-study BGL and EEG activity	239
6.4 Discussion.....	241
6.4.1 Associations between BP and EEG activity (T1DM and T2DM).....	241
6.4.2 Associations between BP and EEG activity (HTN)	242
6.4.3 Associations between BGL and EEG activity (T1DM and T2DM).....	246
6.5 Conclusions	251
Chapter 7 – Limitations, Future Directions, and Conclusions.....	253
7.1 Limitations and Future Directions	253
7.2 Conclusions.....	261
Chapter 8 – Appendices	265
8.1 Consent Form (Non-clinical and Clinical)	265
8.2 Emergency Protocol.....	266
8.3 Chronic Disease Questionnaire (Diabetes Mellitus).....	268
8.4 Chronic Disease Questionnaire (Hypertension)	270
8.5 Cognitive Profile.....	272
8.6 Study Summary Sheet.....	273
8.7 Recruitment Poster.....	274
8.8 Participant Remuneration Form (Clinical only)	275
8.9 Breakdown of glucose-lowering medication	276
8.10 Breakdown of anti-hypertensive medication	277
Chapter 9 – References	278

VI. List of Figures

Figure 1.1 – Life expectancy by birth and sex (1886-2016)	1
Figure 1.2 – Estimated number of Australians categorised by age group in 2018.....	3
Figure 1.3 – Predicted number of Australians over the age of 65 years categorised by age group (2016-2096)	3
Figure 1.4 – Lateral view of the cerebral cortex	6
Figure 1.5 – Diagnostic criteria used to diagnose mild cognitive impairment.....	8
Figure 1.6 – Hypothetical trajectories in normal brain ageing.....	10
Figure 1.7 – Projected prevalence of dementia in Australians (2016-2056).....	12
Figure 1.8 – Diagnostic criteria used to diagnose major neurocognitive disorder/dementia..	14
Figure 1.9 – Key cognitive domains detrimentally affected by cognitive disorders.....	14
Figure 1.10 – Healthy brain tissue compared to Alzheimer’s disease brain tissue	17
Figure 1.11 – Brain areas affected in the early stages of Alzheimer’s disease	18
Figure 1.12 – Patterns in the accumulation of neuropathologies in Alzheimer’s disease.....	19
Figure 1.13 – Leading causes of death in Australians (males and females) in 2016	20
Figure 1.14 – Risk factors for cognitive impairment across the lifespan.....	23
Figure 1.15 – Homeostatic regulation of blood glucose concentration.....	25
Figure 1.16 – Impaired regulation of blood glucose concentration in Type 2 diabetes	28
Figure 1.17 – Predicted prevalence of diabetes (20-79 years) in 2019, 2035, and 2045	31
Figure 1.18 – Trends in leading cause of disease in Australia	32
Figure 1.19 – Possible pathophysiological pathways linking Type 2 diabetes to dementia ...	37
Figure 1.20 – Disturbances at the cellular level associated with glucose neurotoxicity	43
Figure 1.21 – Mechanisms linking impaired insulin signalling to Alzheimer’s disease.....	47
Figure 1.22 – The blood-brain barrier	49
Figure 1.23 – Risk factors linked to the development of hypertension.....	52

Figure 1.24 – Disturbances associated with blood-brain barrier breakdown	60
Figure 1.25 – A neurovascular unit	61
Figure 1.26 – Cerebral arteries damaged by hypertension	63
Figure 1.27 – The International 10-20 system of electroencephalography	65
Figure 2.1 – Non-invasive digital blood pressure monitor	89
Figure 2.2 – Posture and seating position for recording blood pressure	90
Figure 2.3 – Blood glucometer and sterile, single-use lancing device	94
Figure 2.4 – Normal postprandial blood glucose level range after a 2-hour fast	94
Figure 2.5 – 32-channel, non-invasive elastic EEG cap	97
Figure 2.6 – Top view of 10-20 system with electrode positions highlighted	98
Figure 2.7 – Electrode gel, sterile syringe, and blunted needle	99
Figure 2.8 – Unprocessed EEG tracing	100
Figure 2.9 – Screenshot of the Stroop Colour Word Test Program	101
Figure 2.10 – The Mini-Mental State Examination (MMSE)	104
Figure 2.11 – Stimulus sheet (Part 2) of the MMSE	105
Figure 2.12 – Participant completing Construction sub-test of the Cognistat	107
Figure 2.13 – The Cognistat cognitive status profile	108
Figure 2.14 – Protocol for the present study	112
Figure 3.1 – Breakdown of groups comprising the total study cohort	118
Figure 4.1 – Positive correlation between age of disease onset and average response time for matched stimuli in the Stroop Test for Type 2 diabetes mellitus	136
Figure 4.2 – Negative correlation between post-study blood glucose level and total Mini Mental State Examination score for the non-clinical group	138
Figure 4.3 – Positive correlation between post-study diastolic blood pressure and judgement performance in the Cognistat for Type 1 diabetes mellitus	140

Figure 4.4 – Positive correlation between post-study systolic blood pressure and construction performance in the Cognistat for Type 2 diabetes mellitus	142
Figure 4.5 – Positive correlation between post-study diastolic blood pressure and judgement performance in the Cognistat for Type 2 diabetes mellitus	143
Figure 4.6 – Positive correlation between post-study diastolic blood pressure and total Cognistat score for Type 2 diabetes mellitus	144
Figure 4.7 – Negative correlation between pre-study blood glucose level and the attention domain of the Cognistat for Type 2 diabetes mellitus	145
Figure 4.8 – Negative correlation between pre-study blood glucose level and the similarities domain of the Cognistat for Type 2 diabetes mellitus	146
Figure 5.1 – Positive correlation between pre-study systolic blood pressure and alpha power at T ₇ during the baseline phase for the non-clinical group	162
Figure 5.2 – Positive correlation between pre-study systolic blood pressure and beta power at FT ₈ during the baseline phase for the non-clinical group	163
Figure 5.3 – Positive correlation between pre-study systolic blood pressure and alpha power at FC ₃ during the active phase for the non-clinical cohort.....	166
Figure 5.4 – Positive correlation between pre-study systolic blood pressure and gamma power at FC ₃ during the active phase for the non-clinical group	167
Figure 5.5 – Positive correlation between post-study systolic blood pressure and gamma power at FP ₂ during the active phase for the non-clinical group	170
Figure 5.6 – Positive correlation between pre-study diastolic blood pressure and alpha power at P _Z during the baseline phase for the non-clinical group	172
Figure 5.7 – Positive correlation between post-study diastolic blood pressure and gamma power at FP ₂ during the active phase for the non-clinical group.....	175

Figure 5.8 – Positive correlation between pre-study blood glucose level and beta power at F ₃ during the baseline phase for the non-clinical group	177
Figure 5.9 – Negative correlation between pre-study blood glucose level and theta power at F _Z during the active phase for the non-clinical group.....	179
Figure 5.10 – Negative correlation between post-study blood glucose level and theta power at C _Z during the active phase for the non-clinical cohort	181
Figure 5.11 – The association between cerebral blood flow and EEG activity	185
Figure 5.12 – Example of an EEG tracing recorded during euglycaemia and hypoglycaemia in the same individual	187
Figure 6.1 – Negative correlation between pre-study systolic blood pressure and theta power at FT ₇ during the active phase for Type 1 diabetes mellitus.....	193
Figure 6.2 – Negative correlation between pre-study systolic blood pressure and delta power at FT ₇ during the active phase for Type 1 diabetes mellitus.....	194
Figure 6.3 – Negative correlation between pre-study diastolic blood pressure and theta power at FT ₇ during the baseline phase for Type 1 diabetes mellitus	196
Figure 6.4 – Positive correlation between pre-study blood glucose level and theta power at FP ₁ during the baseline phase for Type 1 diabetes mellitus	199
Figure 6.5 – Positive correlation between pre-study blood glucose level and theta power at O _Z during the active phase for Type 1 diabetes mellitus	201
Figure 6.6 – Positive correlation between post-study diastolic blood pressure and gamma power at FC ₃ during the active phase for Type 1 diabetes mellitus.....	205
Figure 6.7 – Negative correlation between post-study blood glucose level and theta power at TP ₇ during the baseline phase for Type 1 diabetes mellitus	208
Figure 6.8 – Negative correlation between post-study blood glucose level and theta power at P ₈ during the active phase for Type 1 diabetes mellitus	210

Figure 6.9 – Positive correlation between glycosylated haemoglobin and delta power at T ₇ during the active phase for Type 1 diabetes mellitus.....	213
Figure 6.10 – Negative correlation between pre-study systolic blood pressure and delta power at O ₂ during the baseline phase for Type 2 diabetes mellitus	215
Figure 6.11 – Positive correlation between pre-study SBP and gamma power at P ₃ during the active phase for Type 2 diabetes mellitus	217
Figure 6.12 – Negative correlation between post-study systolic blood pressure and beta power at C ₄ during the baseline phase for Type 2 diabetes mellitus	219
Figure 6.13 – Positive correlation between pre-study blood glucose level and delta power at TP ₈ during the active phase for Type 2 diabetes mellitus.....	223
Figure 6.14 – Positive correlation between disease duration and gamma power at FT ₇ during the active phase for Type 2 diabetes mellitus	228
Figure 6.15 – Positive correlation between pre-study systolic blood pressure and theta power at P _Z during the baseline phase for hypertension	230
Figure 6.16 – Positive correlation between pre-study diastolic blood pressure and theta power at TP ₇ during the baseline phase for hypertension.....	235
Figure 6.17 – Negative correlation between post-study diastolic blood pressure and gamma power at FT ₇ during the active phase for hypertension	238
Figure 7.1 – Framework for diagnosing and evaluating cognitive dysfunction in Type 2 diabetes mellitus.....	262

VII. List of Tables

Table 1.1 –	Key disease characteristics of type 1 and type 2 diabetes mellitus.....	30
Table 1.2 –	Brain waves commonly observed in an electroencephalogram and their corresponding psychophysiological state(s)	68
Table 1.3 –	Summary of main findings from studies exploring EEG activity in diabetes mellitus.....	75
Table 2.1 –	Blood pressure exclusion and inclusion limit thresholds.....	92
Table 2.2 –	Maximum achievable scores and domain-specific impairment threshold scores or each cognitive domain of the Cognistat	111
Table 3.1 –	Key demographic characteristics for all groups.....	121
Table 3.2 –	Pre-study and post-study cardiovascular variables as well as the change that occurred for each group	124
Table 3.3 –	Pre-study and post-study BGL as well as the change that occurred for each group	126
Table 3.4 –	Disease-specific variables solicited from the clinical groups	127
Table 4.1 –	Mean scores obtained by each group in the Mini-Mental State Examination ..	130
Table 4.2 –	Mean scores obtained by each group for individual domains of the Cognistat as well as total Cognistat score	131
Table 4.3 –	Mean average response times obtained by each group for matched and mismatched stimuli of the Stroop Colour Word Test	134
Table 4.4 –	Associations between disease-specific variables and matched aspects of the Colour Word Test	135
Table 5.1 –	Associations between pre-study SBP and EEG activity during the baseline phase for the non-clinical group.....	161

Table 5.2 –	Associations between pre-study SBP and EEG activity during the active phase for the non-clinical group.....	165
Table 5.3 –	Associations between post-study SBP and EEG activity during the active phase for the non-clinical group.....	169
Table 5.4 –	Associations between pre-study DBP and EEG activity during the baseline phase for the non-clinical group.....	171
Table 5.5 –	Associations between post-study DBP and EEG activity during the baseline phase for the non-clinical group	173
Table 5.6 –	Associations between post-study DBP and EEG activity during the active phase for the non-clinical group.....	174
Table 5.7 –	Associations between pre-study BGL and EEG activity during the baseline phase for the non-clinical group.....	176
Table 5.8 –	Associations between pre-study BGL and EEG activity during the active phase for the non-clinical group.....	178
Table 5.9 –	Associations between post-study BGL and EEG activity during the active phase for the non-clinical group.....	180
Table 6.1 –	Associations between pre-study SBP and EEG activity during the baseline phase for the T1DM group.....	191
Table 6.2 –	Associations between pre-study SBP and EEG activity during the active phase in the T1DM group	192
Table 6.3 –	Associations between pre-study DBP and EEG activity during the baseline phase for the T1DM group.....	195
Table 6.4 –	Associations between pre-study DBP and EEG activity during the active phase for the T1DM group.....	197

Table 6.5 – Associations between pre-BGL and EEG activity during the baseline phase for the T1DM group	198
Table 6.6 – Associations between pre-BGL and EEG activity during the active phase for the T1DM group	200
Table 6.7 – Associations between post-study SBP and EEG activity during the baseline phase for the T1DM group.....	202
Table 6.8 – Associations between post-study SBP and EEG activity during the active phase for the T1DM group.....	203
Table 6.9 – Associations between post-study DBP and EEG activity during the baseline phase for the T1DM group.....	204
Table 6.10 – Associations between post-study DBP and EEG activity during the active phase for the T1DM group.....	204
Table 6.11 – Associations between post-study BGL and EEG activity during the baseline phase for the T1DM group.....	207
Table 6.12 – Associations between post-study BGL and EEG activity during the active phase for the T1DM group.....	209
Table 6.13 – Associations between disease-specific variables (HbA1c, disease duration) and EEG activity during the baseline phase for the T1DM group	211
Table 6.14 – Associations between disease-specific variables (HbA1c, disease duration) and EEG activity during the active phase for the T1DM group.....	212
Table 6.15 – Associations between pre-study SBP and EEG activity during the baseline phase for the T2DM group.....	214
Table 6.16 – Associations between pre-study SBP and EEG activity during the active phase for the T2DM group.....	216

Table 6.17 – Associations between post-study SBP and EEG activity during the baseline phase for the T2DM group.....	218
Table 6.18 – Associations between post-study SBP and EEG activity during the active phase for the T2DM group.....	220
Table 6.19 – Associations between pre-study DBP and EEG activity during the baseline phase for the T2DM group.....	221
Table 6.20 – Associations between pre-study BGL and EEG activity during the baseline phase for the T2DM group.....	222
Table 6.21 – Associations between pre-study BGL and EEG activity during the active phase for the T2DM group.....	222
Table 6.22 – Associations between glycosylated haemoglobin (HbA _{1c}) and EEG activity during the baseline phase for the T2DM group.....	225
Table 6.23 – Associations between glycosylated haemoglobin (HbA _{1c}) and EEG activity the active phase for the T2DM group.....	226
Table 6.24 – Associations between disease duration and EEG activity during the active phase for the T2DM group.....	227
Table 6.25 – Associations between pre-study SBP and EEG activity during the baseline phase for the HTN group.....	229
Table 6.26 – Associations between pre-study SBP and EEG activity during the active phase for the HTN group.....	231
Table 6.27 – Associations between post-study SBP and EEG activity during the baseline phase for the HTN group.....	232
Table 6.28 – Associations between post-study SBP and EEG activity during the active phase for the HTN group.....	233

Table 6.29 – Associations between pre-study DBP and EEG activity during the baseline phase for the HTN group	234
Table 6.30 – Associations between post-study DBP and EEG activity during the baseline phase for the HTN group	236
Table 6.31 – Associations between post-study DBP and EEG activity during the active phase for the HTN group	237
Table 6.32 – Associations between pre-study BGL and EEG activity during the active phase for the HTN group	239
Table 6.33 – Associations between post-study BGL and EEG activity during the active phase for the HTN group	240

VIII. Abbreviations

α – Alpha

A β – Amyloid-beta

AChEI – Acetylcholinesterase Inhibitor

AD – Alzheimer’s Disease

ADA – American Diabetes Association

AgCl – Silver Chloride

AGE – Advanced Glycation End Product

AIHW – Australian Institute of Health & Welfare

APOE – Apolipoprotein E gene

ARC – Arcuate Nucleus

β – Beta

BBB – Blood-Brain Barrier

BGL – Blood Glucose Level

BMI – Body Mass Index

BP – Blood Pressure

BPM – Beats per Minute

CBF – Cerebral Blood Flow

CGM – Continuous Glucose Monitoring

CKD – Chronic Kidney Disease

CNS – Central Nervous System

CPP – Cerebral Perfusion Pressure

CSF – Cerebrospinal Fluid

CVD – Cardiovascular Disease

DBP – Diastolic Blood Pressure

DC – Direct Current

DCCT – Diabetes Control and Complications Trial

DL – Dorsolateral

DM – Diabetes Mellitus

DPP4i – Dipeptidyl Peptidase-4 Inhibitor

DSM – Diagnostic & Statistical Manual of Mental Disorders

ECoG – Electro-Corticography

EEG – Electroencephalography

EOAD – Early Onset Alzheimer’s Disease

EOG – Electro-oculogram

ERP – Event Related Potential

fAD – Familial Alzheimer’s Disease

FFT – Fast Fourier Transform

FPG – Fasting Plasma Glucose

fMRI – Functional Magnetic Resonance Imaging

GLUT-1 – Glucose Transporter 1

HbA_{1c} – Glycosylated Haemoglobin

HR – Heart Rate

HR – Hazard Ratio

HREC – Human Research Ethics Committee

HTN – Hypertension

Hz – Hertz

IDE – Insulin Degrading Enzyme

IDF – International Diabetes Federation

IR – Insulin Resistance

K Ω – Kilo-ohms

LAQ – Lifestyle Appraisal Questionnaire

LTP – Long-Term Potentiation

MANCOVA – Multiple Analysis of Covariance

MCI – Mild Cognitive Impairment

mm Hg – Millimetres of mercury

mmol/L – Millimoles per litre

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

MRI – Magnetic Resonance Imaging

Ms – Milliseconds

$\mu\text{V}/\text{s}^2$ – Microvolts per second squared

NFT – Neurofibrillary Tangles

NRU – Neuroscience Research Unit

NSW – New South Wales

PAD – Peripheral Arterial Disease

PNS – Peripheral Nervous System

PSEN1 – Presenilin 1

PSEN2 – Presenilin 2

PVN – Paraventricular Nucleus

RCT – Randomised Controlled Trial

ROS – Reactive Oxygen Species

RR – Relative Risk

r – rho value

sAD – Sporadic Alzheimer’s Disease

SBP – Systolic Blood Pressure

SD – Standard Deviation

SGLT2i – Sodium Glucose Co-Transporter-2 Inhibitor

SNR – Signal-to-Noise Ratio

SVD – Small Vessel Disease

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

UKPDS – United Kingdom Prospective Diabetes Study

UTS – University of Technology Sydney

VaD – Vascular Dementia

VCI – Vascular Cognitive Impairment

VMPCF – Ventromedial Prefrontal Cortex

VMH – Ventromedial Hypothalamus

WAIS-R – Weschler Adult Intelligence Scale Revised

WHR – Waist-Hip Ratio

WMH – White Matter Hyperintensities

$>$ – greater than

\geq – greater than or equal to

$<$ – less than

\leq – less than or equal to

IX. Abstract

Diabetes mellitus (DM) (Type 1 (T1DM) and Type 2 (T2DM)) and hypertension (HTN) are associated with subtle cognitive dysfunction; however, few studies have explored the cognitive and electroencephalography (EEG) changes that occur in these conditions. The present cross-sectional study assessed cognitive performance (global and domain-specific) in clinical (T1DM, T2DM, and HTN) and non-clinical samples using established cognitive assessments and EEG, and investigated their associations with blood pressure (systolic (SBP) and diastolic (DBP)) and blood glucose level (BGL).

Results were obtained from 94 study participants divided into four groups: non-clinical ($n = 49$), T1DM ($n = 13$), T2DM ($n = 17$), and HTN ($n = 15$). The experimental protocol was commenced by obtaining pre-study BP measurements and a BGL measurement. Participant lifestyle factors and disease-specific variables (*e.g.* HbA1c, age of disease onset, *etc.*) were obtained using the Lifestyle Appraisal Questionnaire (LAQ) and disease-specific questionnaires, respectively. Brain activity was then measured using a 32-channel EEG over two five-minute study phases (baseline (quiet sitting) and active (Stroop Test)). Subsequently, two reliable and validated cognitive screening tools were administered, the Mini-Mental State Examination (MMSE) and the Cognistat. The study was concluded with post-study BP measurements and a BGL measurement.

No significant difference was found in global or domain-specific cognitive performance between the groups. In the non-clinical group, post-study BGL was inversely associated with total MMSE score ($p < 0.05$; $r = - 0.32$). In the T1DM and T2DM groups, higher BGL was significantly associated ($p < 0.05$) with theta activity in anterior brain regions, while glycosylated haemoglobin (HbA_{1c}) and disease duration were found to be significantly associated ($p < 0.05$) with slow-wave oscillations. In the HTN group, higher SBP and DBP was significantly associated ($p < 0.05$) with slow-wave activities over central and parietal brain areas.

These findings provide novel insight into the associations between blood pressure (SBP and DBP) and BGL and EEG activity in non-clinical and clinical groups. The data obtained suggest that the EEG can consistently detect changes in oscillatory brain activity linked to small changes in BP and BGL, identifying the EEG as a potential neurophysiological instrument for early screening for the subtle changes in cognition linked to both DM and HTN. Future use of EEG as a screening tool could avert adverse cognitive outcomes linked to these chronic diseases, such as Alzheimer's disease (AD) and dementia, and help reduce the substantial socioeconomic and emotional burden associated with them.