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.

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Production Note:
Signature: Signature removed prior to publication.

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II. Acknowledgements

This thesis has been the most significant and exacting undertaking of my professional career, requiring sustained self-discipline, determination, and resilience. The individuals mentioned below merit appreciable praise; they contributed to maintaining not only my sanity, but also the final polished version of this thesis. Words alone are insufficient to reflect my appreciation of them.

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I am immeasurably grateful and indebted to Dr Elizabeth Louise May, who proofread the thesis and provided substantial editing input. Her uncompromising standards for writing emboldened me to become a stickler for proper English, using every word and comma with precision and economy, and to consult the acknowledged authority (Fowler's Modern English Usage) for all matters concerning English usage whenever uncertain. It is my hope that the examiners enjoy reading this dissertation half as much as they did reading hers.

I would also like to extend sincere appreciation to the professional organisations, Diabetes Australia, Diabetes New South Wales (NSW), and Alzheimer's Australia, for supporting and promoting the research and facilitating recruitment of the clinical groups. Although these groups were difficult to recruit, I take pride in knowing this research may, infinitesimally and indirectly, someday benefit people living with diabetes mellitus (Type 1 and Type 2) and hypertension. Importantly, I hope it spotlights the need for continued research into these challenging and prevalent chronic diseases.

Considerable thanks are also due for my colleagues in the Neuroscience Research Unit (NRU). They inspired me to persevere in light of the highs and lows of academia, listened to countless seminar practice sessions, and helped maintained my marbles over numerous lunch outings. I also owe tremendous thanks to all study volunteers who participated in the study – whether immediate family, friends, or strangers. Without their involvement (and their enthusiasm and interest), this research would not have been possible or have advanced.

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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.
2. **Kalatzis, G.,** Lees, T., Nassif, N., Zaslawski, C., & Lal. S. Exploring cognitive function in diabetes and non-diabetes samples using electroencephalography (EEG) and psychometric assessment: A comparative study. Oral presentation: The 37th Annual Scientific Meeting of the Australasian Neuroscience Society 2017, Sydney, 3rd – 6th December.
3. **Kalatzis, G.,** Lees, T., Nassif, N., Zaslawski, C., & Lal, S. Investigating cognitive function in diabetes and healthy samples using electroencephalography (EEG) and psychometric assessment: a comparative study. Oral presentation: The Inter-University Neuroscience & Mental Health Conference 2016, Sydney, 20th – 21st September.
4. **Kalatzis, G.,** Lees, T., Nassif, N., Zaslawski, 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: 10.1111psyp.12495.
6. Lees, T., **Kalatzis, G.,** & Lal, S. Examining negative mental states and their association to psychometric and electroencephalographic measures of cognitive performance in Australian Nurses. Poster presentation: 55th Annual meeting of the Society for Psychophysiological Research 2015, Seattle, USA.

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., Zaslawski, 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

VI. List of Figures

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VIII. Abbreviations

α – Alpha

Aβ – 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

$HbA1_C$ – 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

KΩ – 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

$\mu V/s^2$ – 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

VMPFC – 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 ($HbA1_C$) 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.