EFFECTS OF ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION OVER THE MOTOR CORTEX ON RESPONSE PROCESSING.

Alexander Christian Conley

B Psychology (Hons)

Submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy (Psychology).

Faculty of Science and Information Technology

University of Newcastle, Australia

September, 2016

Statement of Originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

Statement of Collaboration

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

Statement of Authorship

I hereby certify that the work embodied in this thesis contains a published paper/s/scholarly work of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publication/s/scholarly work.

Alexander C. Conley

Publications

Publications arising from this thesis

Marquez, J., **Conley, A.C.**, Karayanidis, F., Lagopoulos, J. & Parsons, M.W. 2015. Anodal direct current stimulation in the healthy aged: effects determined by the hemisphere stimulated. Restorative Neurology and Neuroscience, 33, 509-519. doi: 10.3233/RNN-140490.

Conley, A.C., Marquez, J., Parsons, M.W., Fulham, W.R., Heathcote, A. & Karayanidis, F. 2015. Anodal tDCS over the Motor Cortex on Prepared and Unprepared Responses in Young Adults. PLOS One, DOI: 10.1371/journal.pone.0124509.

Conley, A.C., Fulham, W.R., Marquez, J., Parsons, M.W. & Karayanidis, F. Under Revision, May 2016. No effect of anodal transcranial direct current stimulation over the motor cortex on response-related ERPs during a conflict task. Frontiers in Human Neuroscience.

Conley, A.C., Marquez, J. Fulham, W.R., Parsons, M.W. & Karayanidis, F. Manuscript in preparation. Effects of transcranial direct current stimulation over the sensorimotor areas of chronic stroke patients on response processes.

Conference presentations arising from this thesis

Conley, A.C., Marquez, J., Parsons, M.W., Fulham, W.R., Heathcote, A. & Karayanidis, F. 2015. Online vs offline effects of anodal transcranial direct current stimulation on response speed. Brain Stimulation, 8 (2), DOI: 10.1016/j.brs.2015.01.165. At the 1st International Brain Stimulation, Singapore 2015.

Conley, A.C., Marquez, J., Wong, A.S.W., Cooper, P., Parsons, M.W., Karayanidis, F. 2015. Effect of anodal tDCS on cortical activation during response preparation and activation. Frontiers in Human Neuroscience, DOI: 10.3389/conf.fnhum.2015.217.00184. At the 14th International Conference on Cognitive Neuroscience, Brisbane 2014.

Conley, A.C., Fulham, W.R., Parsons, M., Karayanidis, F. 2013. Effects of anodal transcranial direct current stimulation on responding in healthy younger adults. Frontiers in Human Neuroscience, DOI: 10.3389/conf.fnhum.2013.212.00122. At the 2013 Australasian Cognitive Neuroscience Conference, Melbourne.

Conley, A.C., Marquez, J., Parsons, M.W., Fulham, W.R., Lagopoulos, J., Karayanidis, F. 2012. Sustained effects of anodal tDCS over the dominant motor cortex on response preparation processes. Frontiers in Human Neuroscience, DOI: 10.3389/conf.fnhum.2012.208.00027. At the 2012 Australasian Cognitive Neuroscience Conference, Brisbane.

Conley, A.C., Marquez, J., Parsons, M.W., Lagopoulos, J., Karayanidis, F. 2012. Effects of anodal tDCS over the primary motor cortex on response preparation and execution. Presented at the 39th Australasian Experiment Psychology Conference, University of New South Wales, Sydney, 2012.

Conley, A.C., Marquez, J., Parsons, M.W., Lagopoulos, J., Karayanidis, F. 2011. Effects of Anodal tDCS over the Primary Motor Cortex on Motor Function and Response Mechanisms. Presented at the 21st Annual meeting of the Australasian Society for Psychophysiology, Macquarie University, 2011.

Statement of Contribution

I attest that Research Higher Degree candidate Alexander C. Conley made the following contributions to each of the papers that are submitted as part of his PhD thesis. Papers are listed below in the order they appear in this thesis followed by an outline of co-author contribution.

Associate Professor Frini Karayanidis

Date: 12/09/2016

Associate Professor Jim Lagopoulos

Date: 31/08/2016

Professor Mark W. Parsons

Date: 31/08/2016

Mrs. Jodie L. Marquez

Date: 01/09/2016

Professor Andrew J. Heathcote

Date: 31/08/2016

Dr. W. Ross Fulham

Date: 02/09/2016

Endorsed by: Associate Professor Frances Martin

ADRT

Date: 12/09/2016

Mr. Alexander C. Conley

Date: 01/09/2016

Marquez, J., **Conley, A.C.**, Karayanidis, F., Lagopoulos, J. & Parsons, M.W. 2015. Anodal direct current stimulation in the healthy aged: effects determined by the hemisphere stimulated. Restorative Neurology and Neuroscience, 33, 509-519. doi: 10.3233/RNN-140490.

A.C. Conley collected data, ran the statistical and ERP analyses, and assisted with the preparation of the manuscript. J. Marquez collected data and took the lead in writing the manuscript. F. Karayanidis contributed to the design of the analyses, and the preparation of the manuscript. J. Lagopoulous contributed to the preparation of the manuscript. M.W. Parsons contributed to the preparation of the manuscript.

Conley, A.C., Marquez, J., Parsons, M.W., Fulham, W.R., Heathcote, A. & Karayanidis, F. 2015. Anodal tDCS over the Motor Cortex on Prepared and Unprepared Responses in Young Adults. PLOS One, DOI: 10.1371/journal.pone.0124509.

A.C. Conley collected the data, ran the data analysis and took the lead in writing the manuscript. J. Marquez assisted in the preparation of the manuscript. M.W. Parsons assisted in the preparation of the manuscript. W.R. Fulham assisted with data analysis and the preparation of the manuscript. A. Heathcote assisted with data analysis and the preparation of the manuscript. F. Karayanidis contributed to the research design and the preparation of the manuscript.

Conley, A.C., Fulham, W.R., Marquez, J., Parsons, M.W. & Karayanidis, F. 2016. No effect of anodal transcranial direct current stimulation over the motor cortex on response-related ERPs during a conflict task. Frontiers in Human Neuroscience. 10:384. doi: 10.3389/fnhum.2016.00384.

A.C. Conley collected the data, ran the data analysis and took the lead in writing the manuscript. W.R. Fulham assisted with data analysis and the preparation of the manuscript. J. Marquez collected the data and assisted with the preparation of the manuscript. M.W. Parsons assisted with the preparation of the manuscript. F. Karayanidis contributed to the research design and the preparation of the manuscript.

Conley, A.C., Marquez, J. Fulham, W.R., Parsons, M.W. & Karayanidis, F. Manuscript in preparation. Effects of transcranial direct current stimulation over the sensorimotor areas of chronic stroke patients on response processes.

A.C. Conley collected the data, ran the data analysis and took the lead in writing the manuscript. J. Marquez collected the data and assisted with the preparation of the manuscript. W.R. Fulham assisted with data analysis and the preparation of the manuscript. M.W. Parsons assisted with the preparation of the manuscript. F. Karayanidis contributed to the research design and the preparation of the manuscript.

Acknowledgements and Dedications

This thesis was supported by a University of Newcastle Central Research Scholarship.

Firstly, I would like to thank my supervisors, Associate Professor Frini Karayanidis and Professor Mark Parsons for their continued support and guidance over the course of my research degree. I hope that this is but the start of many positive collaborative projects which we will work on together. Secondly I would like to thank Emeritus Professor Pat Michie, Professor Andrew Heathcote and Dr. Ross Fulham for their assistance with analysis, and their helpful advice on my writing. In addition I would like to thank Jodie Marquez for being the "other soldier in the trenches" during the data collection.

I am thankful to all the members of the Functional Neuroimaging Laboratory. In particular I would to thank Todd Jolly and Alexander Provost for their excellent training, Tony Kemp and Gavin Cooper for technical assistance, and also to Jaime Rennie, James Miller and Sascha Isaacs for their assistances with data collection. In addition I would like to thank Patrick Cooper and Aaron Wong for their continuous support throughout the period of my candidature.

Finally I would like to thank all the participants who volunteered their time and effort to contribute to the research enclosed in this document.

I dedicate this document to my friends and family who supported me over the duration of this journey.

Table of Contents

Publications ..... **iii**

Statement of Contribution ..... **iv**

Acknowledgements and Dedications ..... **vi**

Table of Contents ..... **vii**

Abstract ..... **xi**

Abbreviations ..... **xii**

Thesis Overview ..... **xiii**

Chapter 1: Effects of Transcranial Direct Current Stimulation over the Motor Cortex **1**

1.1: Introduction to Transcranial Direct Current Stimulation 1

1.1.1: Description of Transcranial Direct Current Stimulation 1

1.1.2: Animal Studies 2

1.1.3: Proposed clinical benefits of tDCS 5

1.2: tDCS over the Motor Cortex in Humans 6

1.2.1: Effects on Motor Excitability - Initial Investigations/Breakthrough 6

1.2.2: Neural basis of tDCS effects - Pharmacological studies 8

1.2.3: tDCS Studies on Motor Excitability 9

1.2.4: Functional Performance Following Anodal tDCS 11

1.2.5: Application of tDCS over M1 in stroke patients 13

1.2.6: Psychophysiological Performance Following Anodal tDCS 14

Chapter 2: Electroencephalography and Event-Related Potentials **20**

2.1: Contingent Negative Variation 21

2.1.1: Components of the CNV 22

2.1.2: Task Properties and the CNV 22

2.2: Lateralised Readiness Potential 24

2.2.1: Stimulus Locked Lateralised Readiness Potential 25

2.2.2: Response Locked Lateralised Readiness Potential 26

2.3: The P300 27

2.4: tDCS effects on ERPs 28

2.6: Conclusion – Rationale for papers 29

Chapter 3: Anodal direct current stimulation in the healthy aged: effects determined by the hemisphere stimulated. **33**

3.1: Introduction 33

3.2: Methods 35
3.2.1: Subjects 35
3.2.2: Study design 36
3.2.3: tDCS 37
3.2.4: Data analysis 38
3.3: Results 39
3.3.1 Participant characteristics 39
3.3.2: Functional Motor Measures 40
3.3.3: Go/Nogo Task Behavioural Results 43
3.3.4: Electrophysiological Results 44
3.3.5: Participant tolerance 44
3.4: Discussion 44
3.4.1: Major findings 44
3.4.2: Limitations 47
3.4.3: Clinical implications 48
3.4.4: Conclusion 48
Chapter 4: Anodal tDCS over the motor cortex on prepared and unprepared responses in young adults. 50
4.1: Introduction 50
4.1.1: Effects of tDCS on M1 51
4.1.2: Present Study 52
4.2: Experiment 1 53
4.2.1: Methods 53
4.2.2: Results 56
4.2.3: Discussion 58
4.3: Experiment 2 60
4.3.1: Methods 60
4.3.2: Results and Discussion 60
4.4: Experiment 3 61
4.4.1: Methods 62
4.4.2: Results 62
4.4.3: Discussion 63
4.5: Bayesian analyses across the three experiments 64
4.6: General Discussion 65

Chapter 5: No effect of anodal transcranial direct current stimulation over the motor cortex on response-related ERPs during a cued go/nogo task. ... 69

5.1: Introduction ... 69

5.2: Experiment 1 ... 74

5.2.1: Method ... 75

5.2.2: Results ... 81

5.2.3: Discussion ... 86

5.3: Experiment 2 ... 86

5.3.1: Method ... 87

5.3.2: Results ... 88

5.3.3: Discussion ... 92

5.4: Bayesian Analysis ... 92

5.5: General Discussion ... 94

Chapter 6: Effects of transcranial direct current stimulation over the sensorimotor areas on response processes in chronic stroke patients. ... 97

6.1: Introduction ... 97

6.2: Methods ... 101

6.2.1: Patients ... 101

6.2.2: Design ... 102

6.2.3: EEG and Data Analysis ... 104

6.3: Results ... 104

6.3.1: Behavioural ... 104

6.3.2: Electrophysiological Results ... 105

6.4: Discussion ... 107

Chapter 7: General Discussion ... 110

7.1: Overview of findings ... 110

7.2: Implications for effectiveness of tDCS of motor cortex ... 112

7.3: Implications for anodal tDCS in ageing and clinical samples ... 115

7.4: Methodological considerations ... 116

7.4.1: Effectiveness of the go/nogo task ... 116

7.4.2: Suitability of the stimulation parameters ... 117

7.5: Spread of electrical field of anodal tDCS interventions ... 118

7.6: Is there evidence that tDCS is more effective at enhancing cognitive compared to motor function? ... 120

7.7: Future directions and final comments ... 121

Chapter 8: References 123

Abstract

Anodal transcranial direct current stimulation (tDCS) is the non-invasive application of a stimulating current which has been proposed as a possible intervention technique for a number of pathologies that affect the motor system, including Parkinson's disease and stroke. When applied over the motor cortices, anodal tDCS has been shown to elicit long lasting changes to motor excitability. Application of anodal tDCS over the motor cortex has also been shown to improve performance on functional motor tasks. However, there is little knowledge of how anodal tDCS produces these changes. This thesis investigates whether anodal tDCS over the motor cortex influences responding, and if so how are response processes changed. This is explored across functional motor performance, as well as behavioural and electrophysiological performance on a cued go/nogo task with informative and uninformative cues. These experimental outcomes are assessed on three different subject groups, healthy young and older adults, as well as chronic stroke patients. The analysis of the results showed that while there was a small improvement of gross motor performance following anodal tDCS in healthy older adults, there was no beneficial effect of stimulation on either behavioural or electrophysiological data. This null effect was consistent across all three subject groups. Bayesian analyses confirmed that null effects models of the data were stronger fits compared to models which included an effect of stimulation. These results indicate that the application of anodal tDCS over the motor cortex does not impact response processes, which calls into question the efficacy of using anodal tDCS as a therapeutic intervention.

Abbreviations

Abbreviation	Meaning
ADM	Abductor digiti minimi
ANOVA	Analysis of variance
BDNF	Brain derived neurotrophic factor
BP	Berietschaftspotential
Ca^+	Calcium ions
CNS	Central-Nervous System
CNV	Contingent negative variation
CTI	Cue-target interval
CYC	Cycloserine
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
ECT	Electro-cortical therapy
EEG	Electroencephalography
EMG	Electro-myography
EOG	Electro-oculogram
ERP	Event-related potential
FDI	First dorsal interosseous
FMS	Fugl-Meyer Scale
GABA	γ-amino-butyric acid
HEOG	Horizontal electro-oculogram
JTT	Jebsen Taylor Hand Function Test
LRP	Lateralised readiness potential
LTP	Long-term potentiation
mA	Milliamp
M1	Primary motor cortex
MEP	Motor-evoked potential
MoCA	Montreal Cognitive Assessment
MRS	Modified Rankin Scale
NMDA	N-methyl d-aspartate
RT	Reaction time
SMA	Supplementary motor area
SRTT	Serial reaction time task
SSRT	Stop-signal reaction time
SST	Stop-signal task
TA	Tibialis anterior
tDCS	Transcranial direct current stimulation
TEP	TMS-evoked potential
TMS	Transcranial magnetic stimulation
µA	Microamp
µV	Microvolt
VEOG	Vertical electro-oculogram

Thesis Overview

Transcranial direct current stimulation or tDCS is a non-invasive brain stimulation technique which generates a weak electrical field between two electrodes placed on the scalp. Depending on the placement of the electrodes, this electrical field has been shown to depolarise or hyperpolarise underlying cortical areas. Research showing that tDCS can facilitate motor excitability has led to interest in tDCS as a possible clinical intervention technique for a number of pathologies including Parkinson's disease and post-stroke rehabilitation. However, as interest in the technique has been increasing, so has the number of studies that show no improvement of performance following the application of tDCS. At present, there is still much we do not know about how tDCS affects cortical excitability, and how these changes impact motor performance.

The aim of this thesis is to investigate the effects of anodal tDCS over the motor cortex on response processes in both healthy younger and older adults, as well as in chronic stroke patients. Although research of the effects of transcranial direct current stimulation in both healthy and clinical samples is increasing, there is still much that is unknown about the mechanisms by which tDCS effects changes in the cortex. In this thesis, we specifically investigate the way in which motor cortex stimulation, which is the most targeted area of use for tDCS, affects specific response processes such as the preparation, selection or activation of a response. These mechanisms, while critical for the engagement of movement, have not yet been adequately investigated. Across four experiments, we assess the likelihood of beneficial changes in behavioural and electrophysiological performance following anodal tDCS over the motor cortex. To isolate these specific processes we have used a cued go/nogo paradigm with informative and non-informative cues. The use of these different cue types allowed the comparison of different levels of preparation, while the choice between two different target types on each trial allowed for assessment of response selection.

The structure of this thesis is as follows. Chapter 1 describes the properties of tDCS and then outlines the findings of previous experiments that have applied anodal tDCS over the motor cortex. These experiments are separated into a number of categories including those focusing on motor excitability, functional motor performance and also the performance on psychophysiological tasks following anodal tDCS over the motor cortex. There is then a description of the results of studies that have assessed the effectiveness of tDCS over the motor cortex in stroke patients. Following this Chapter 2 discusses the main electrophysiological waveforms (ERPs) that are associated with the response processes that are assessed in the experimental chapters. These ERPs are the contingent negative variation, which indexes response preparation, and the lateralised readiness potential which assesses both response selection and activation, depending on whether it is time-locked to the target or the response. There is also a description of the P300 peak, and its relationship with stimulus evaluation. This chapter ends with an investigation into the effects of the small number of studies that have assessed the impact of anodal tDCS on ERPs. This introduction is followed by four experimental chapters.

Chapter 3 examines whether anodal tDCS over the dominant or non-dominant motor cortex enhances the performance of healthy older adults on functional motor performance on the Jebsen Taylor Hand Function Test (JTT, Jebsen, Taylor, Trieschmann, Trotter & Howard, 1969) and grip force measures, and response speed on a cued go/nogo task. While anodal tDCS over the dominant motor cortex improved JTT performance, there was no impact of stimulation over the non-dominant motor cortex on the JTT. There was no effect of anodal tDCS of either motor cortex on both the grip strength tests, and the performance on the cued go/nogo paradigm.

Chapter 4 examines the behavioural performance of healthy younger adults following anodal tDCS over the dominant motor cortex using the cued go/nogo task. This chapter also

assesses whether there is an impact of the time between stimulation cessation and task completion on the effectiveness of anodal tDCS over the motor cortex. The effect of delay was assessed by comparing behavioural performance when stimulation was applied simultaneously, directly before or approximately 40 minutes before task completion. Analysis showed that there was no impact of anodal tDCS on behavioural performance of the young adults. Additionally, this pattern of results was consistent across all three timing conditions, indicating that there was no effect of the delay between stimulation cessation and task completion on the effectiveness of anodal tDCS. Bayesian analyses confirmed that null models were stronger fits for the data compared to models that included an effect of stimulation.

Chapter 5 examines the effects of anodal tDCS over the motor cortex on electrophysiological components associated with responding. Across two experiments we assess the effectiveness of anodal tDCS at enhancing response preparation, selection and activation in healthy younger (Experiment 1) and older adults (Experiment 2). The analyses of these two experiments display a failure of anodal tDCS over the motor cortex to enhance any response-related ERP waveform. Once again, Bayesian analyses confirm that models that include stimulation are weaker fits of the electrophysiological data compared to null effects models.

The last experimental chapter, Chapter 6, assesses whether there is an effect of tDCS on behavioural and electrophysiological performance of chronic stroke patients. The performance of the patients on the cued go/nogo was assessed following anodal stimulation of the affected motor cortex and also after cathodal stimulation of the unaffected motor cortex. Similar to the results in healthy subjects, neither anodal nor cathodal tDCS elicited changes to cued go/nogo performance that were significantly different from sham.

The final chapter, Chapter 7, is the general discussion of the results and the implications of the four experimental chapters. The consistent finding of null effects following

anodal stimulation over the motor cortex in all subject groups implies that anodal tDCS does not alter either behavioural performance or the processes that are involved in the generation of a response. Moreover, the results of the experimental chapters indicate that single session interventions utilising anodal tDCS over the motor cortex are not appropriate to elicit changes to response processes. In contrast future research should investigate whether multiple sessions, applied in conjunction with training, is able to produce enhancements to response processes.