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Transcranial direct current stimulation: a potential modality for stroke rehabilitation

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Declarations

Statement of Originality

I Jodie Marquez hereby declare that this 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 Authorship

I Jodie Marquez hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of this thesis a written statement from each co-author, and endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Statement of Ethical Conduct

In addition, ethical approval from the Hunter New England Area Health Service Ethics Committee, and co registration from the University of Newcastle Human Ethics Committee was granted for the clinical studies presented in this thesis. In each instance, participants were required to read an information statement and provide informed written consent prior to the collection of any data.

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Publications, Presentations and Awards

Peer Reviewed Publications Included in this Thesis

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Marquez J, Conley A, Karayanidis F, Lagopoulos J, and Parsons M. (2015). Anodal direct current stimulation in the healthy aged: Effects determined by the hemisphere stimulated. *Restorative Neurology and Neuroscience* 33 (4):509-19

Marquez J, van Vliet P, McElduff P, Lagopoulos J, Parsons M. (2015).Transcranial direct current stimulation (tDCS): Does it have merit in stroke rehabilitation? A systematic review. *International Journal of Stroke* 10 (3):306-16

Marquez J, Bivard A, Visser M, Lagopoulos J, and Parsons M. (2017). The physiological effects of cathodal and anodal direct current stimulation (tDCS) in older adults. *Functional Neurology*. Under Review.

Additional Peer Reviewed Publications Associated with this Thesis

Conley AC, Fulham WR, **Marquez JL**, Parsons MW, and 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

Conley AC, **Marquez JL**, Parsons MW, Fulham WR, Heathcote A, and Karayanidis F. (2015). Anodal tDCS over the Motor Cortex on Prepared and Unprepared Responses in Young Adults. *PLoS One* 10 (5):e0124509

Marquez J, and Parsons M. (2017). Chapter 26: Electrical and magnetic brain stimulation to enhance recovery post stroke. In: Hankey G. and Saver J. (eds) *Stroke Treatment and Prevention: An Evidenced-Based Approach* (2nd edition). Cambridge University Press. In Press.

Published Abstracts

Marquez J, Parsons M, Stoginovsky E, Conley A, Lagopoulos J, and Karayinidis F. (2014). Transcranial direct current stimulation (tDCS): Anodal or Cathodal stimulation for chronic stroke – which is better? Cerebrovascular Diseases 37:300-300. 23rd *European Stroke Conference, Nice.*

Marquez JL, van Vliet P, McElduff P, Lagopoulos J, Parsons MW. (2013). Transcranial direct current stimulation (tDCS): Is it effective as a stroke therapy? A systematic review. International Journal of Stroke. *SMART Strokes Australasian Nursing and Allied Health Conference, Brisbane.*

Marquez JL, van Vliet P, Miller J, Lagopoulos J, Parsons MW. (2013). Transcranial direct current stimulation (tDCS): A randomised controlled trial to investigate the effects on upper limb function in chronic stroke. International Journal of Stroke. *24th Annual Scientific Meeting of the Stroke Society of Australasia, Darwin.*

Additional Conference Presentations

Conley A, **Marquez J**, Wong A, Cooper P, Parsons M, Karayanidis F. Effect of anodal tDCS on cortical activation during response preparation and activation. *Priority Research Centre for Translational Neuroscience and Mental Health: Postgraduate and Postdoctoral Conference, Newcastle, October 2014*

Conley A, **Marquez J**, Parsons MW, Lagopoulos J, Karayanidis F. Effects of anodal tDCS over the primary motor cortex on response preparation and execution. *39th Australasian Experimental Psychology Conference, Sydney, April 2012.*

Conley AC, **Marquez JL**, Parsons MW, Fulham WR, Lagopoulos J, Karayanidis F. Sustained effects of anodal tDCS over the dominant motor cortex on response preparation processes. ACNS 2012 *Australasian Cognitive Neuroscience Conference. Brisbane, November 2012.*

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Awards

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Early Career Researcher Grant, University of Newcastle 2011 - $9,500

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List of Abbreviations

Activities of daily living	ADLs
Arterial spin labelling	ASL
Blood-oxygenated dependent signal	BOLD
Brain derived neurotrophic factor	BDNF
Central nervous system	CNS
Cerebrospinal fluid	CSF
Constraint induced movement therapy	CIMT
Contingent negative variation	CNV
Cortical silent period	CSP
Diffusion tension imaging	DTI
Dorsolateral prefrontal cortex	DLPFC
Echo time	TE
Echoplanar imaging	EPI
Electroconvulsive therapy	ECT
Electroencephalogram	EEG
Event related potential	ERP
Food and drug administration	FDA
Fuggyl meyer assessment	FM
Functional electrical stimulation	FES
Functional magnetic radiation imaging	fMRI
Glutamate	Glu
Glutamine + glutamate	Glx
High definition direct current stimulation	HD-tDCS
Inositol	Ins
Intra-cortical facilitation	ICF
Intrinsic connectivity contrast	ICC
Jebsen Taylor function test	JTT
Lactate	Lac
Long term potentiation	LTP
Low field magnetic stimulation	LFMS
Magnetic resonance imaging	MRI
Magnetic resonance spectroscopy	MRS
Montreal cognitive assessment	MoCA
Motor evoked potentials	MEPs
N-acetylaspartic acid	NAA
N-methyl-d-aspartate	NMDA
Paired associative stimulation	PAS
Primary motor cortex	M1

Proprioceptive neuromuscular facilitation	PNF
Purdue peg board test	PPBT
Reaction time	RT
Regional cerebral blood flow	rCBF
Repetition time	TR
Repetitive Transcranial magnetic stimulation	rTMS
Resting membrane threshold	RMT
Resting state functional Magnetic resonance imaging	Rs-fMRI
Short interval intra-cortical inhibition	SICI
Simple reaction time	SRT
Supplementary motor area	SMA
Theta burst stimulation	TBS
Total creatin	Cr+Pcr
Transcranial alternating current stimulation	tACS
Transcranial direct current stimulation	tDCS
Transcranial magnetic stimulation	TMS
Transcranial random noise stimulation	tRNS
Voxel-based morphometry	VBM
Wolf motor function test	WMFT

Thesis Abstract

Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive brain stimulation which has been investigated in a broad range of neuropsychiatric conditions and as a method to modulate cognitive performance in healthy individuals. It is generally accepted that the main mechanism by which tDCS modulates brain function is via a neural membrane polarization shift which can, in turn, lead to diverse changes in single neuron, synaptic and network activity (Peterchev, Wagner et al. 2012). However, the direction of polarization shift is sensitive to the stimulation dose, the state of brain activity at the time of stimulation and individual anatomy (Bikson and Rahman 2013). This results in a large inter individual variability to the neurophysiological and behavioural response to tDCS. Given the simplicity of tDCS and the complexity of brain function, we sought to unveil some of the physiological mechanisms underpinning the effects of tDCS in order to better our understanding of the variability in response to tDCS and to allow us to predict those most likely to respond. Ultimately our objective was to direct the translation of the research evidence into therapeutic applications of tDCS for stroke patients.

The aim of this research was to determine the potential application of tDCS in the stroke population. At the commencement of this PhD research project, keen interest in the use of tDCS as a potential therapeutic tool in neuromotor conditions, such as stroke, was emerging. As tDCS is portable, relatively inexpensive, free from major adverse effects, and easily applied concurrently with other interventions, it is ideally suited for use in stroke rehabilitation therapy. The goal of tDCS in stroke is to increase cortical excitability of the lesioned hemisphere and/or reduce excitability on the non-lesioned hemisphere to restore interhemispheric balance (Mordillo-Mateos, Turpin-Fenoll et al. 2012).

The vast majority of literature investigating tDCS has been conducted in young, healthy subject. As stroke patients are typically more senior and have age related changes in cortical structure, function and excitability, we began our investigation into the functional and physiological effects of tDCS in a healthy, aged population. We found that the hemispheres responded differently to tDCS and the response appeared to be task specific, but it was not mediated by age. However, a subsequent multimodal imaging study did not support these findings and failed to reveal a difference when tDCS was applied to the dominant or non-dominant hemisphere but showed that the effects were diffuse and determined by the type of stimulation.

In a systematic review of the stroke literature we synthesised the evidence from 15 studies and confirmed the safety and acceptability of this modality in the stroke population.

We concluded that tDCS may be effective in enhancing motor performance, atleast in the short term. Those most likely to benefit were patients with chronic stroke and/or mild to moderate impairments. However these positive findings were not consistent across all studies and the size of the treatment effect was at best modest and may not translate to clinically meaningful change for some or all patients. We used this evidence to conduct a randomised controlled trial in chronic stroke patients and found that neither anodal nor cathodal stimulation resulted in statistically significant improvement in upper limb performance. A secondary analysis was performed and identified that those with moderate or severe disability responded positively to cathodal stimulation with improved gross motor function.

This thesis, in conjunction with the rapidly growing body of evidence in this field, highlights the inconsistency in the effects of tDCS at both an intraindividual level and between subjects, and the transient nature of these effects which limits the clinical value of this intervention. Further scrutiny of the mechanisms underpinning the effects of tDCS is required for the rational advancement of tDCS as a clinical modality in stroke rehabilitation.