NOVEL ASSESSMENT OF GAIT AND MOBILITY FUNCTION IN TRANSTIBIAL AMPUTEES

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SUMMARY

Lower-limb amputees require extensive rehabilitation to restore gait and mobility function and achieve successful re-integration into the community. Decreasing length of hospital stays and resources shortages have increased the need for more efficient treatment to hasten recovery. However, complex issues such as older age, various levels of amputation and associated comorbidities pose additional challenges to the restoration of gait and mobility function. Much research into lower-limb amputees has focussed on vascular interventions and prosthetic technology, with limited literature investigating alternative approaches to characterise gait and mobility function. A good understanding of issues influencing amputee rehabilitation is necessary to help identify aspects of amputee rehabilitation requiring attention and to drive more effective and efficient rehabilitation approaches. New assessments of gait and mobility function have the potential to progress our understanding of lower-limb amputee rehabilitation. The purpose of this thesis was to investigate novel assessments of gait and mobility function in transtibial amputees. These assessments were investigated from a clinical rehabilitation perspective to determine their potential contribution to future amputee rehabilitation.

There are four sections to this thesis. The first section established the state of amputee rehabilitation in Australia by reviewing contemporary data from amputee rehabilitation services at a national level (n = 6,588), and from a single regional rehabilitation service (n = 531). Trends for increasing length of stay and decreasing age were identified. Many amputees (43.4%) presented with multiple comorbidities. Time to achieve key rehabilitation milestones increased over the period of

observation. These findings identified shifts in patient characteristics which affected the timely and optimal restoration of function by amputee rehabilitation services. New and novel assessments of gait and mobility function may assist future amputee rehabilitation and should be investigated. Greater understanding of amputee gait and mobility may allow for more efficient functional assessments and identify individuals likely to need additional therapy input, assisting rehabilitation units in planning and prioritising treatment.

The second section of the thesis investigated the potential that spatial-temporal gait variability has as a measure of gait function in transtibial amputees. Forty-seven community dwelling amputees were recruited from the single prosthetic rehabilitation facility reviewed in the first section of this thesis. The influence of intra-subject gait speed variability was examined and the variability of speed normalised spatial-temporal gait parameters was calculated for individual participants. Greater normalised gait variability was observed in amputees with a history of falls. This study identified that gait variability may be an important measure of gait function and additionally demonstrated the importance of normalising for walking speed in the analysis of gait variability.

The third section of the thesis investigated wearable technology as a novel method to assess community activity and participation. Amputees recruited for the previous gait variability study also participated in this experiment. Data from an accelerometer based device to assess step counts, and a global positioning system (GPS) to assess community visits, were linked to identify community activity and participation. Measures of activity and participation in the community were negatively associated

with normalised gait variability, further suggesting gait variability is an important clinical marker of gait function.

The final section of the thesis investigated the use of transcranial magnetic stimulation to determine if neurophysiological measures of brain function may assist clinical practice as neural biomarkers of gait function. A subset of community living transtibial amputees who had participated in the previous studies were recruited. A ratio of corticomotor excitability of ipsilateral and contralateral projections to the amputated limb (index of corticospinal excitability, ICE) was calculated. Relatively greater excitability of ipsilateral compared to contralateral projections to motoneurons innervating residual muscles of the amputated limb was associated with increased normalised gait variability. Further investigation of the contribution of ipsilateral and contralateral motor cortex to gait function was conducted in amputees completing prosthetic rehabilitation. Bilateral reorganisation of the motor cortex occurred following lower-limb amputation and continued through prosthetic rehabilitation. Intracortical inhibition within a hemisphere at key phases of rehabilitation was predictive of gait function at discharge. For the contralateral motor cortex, reduced intracortical inhibition at admission to rehabilitation and when undertaking first walk with a prosthetic limb was associated better gait function. However, for the ipsilateral motor cortex, reduced intracortical inhibition at discharge from rehabilitation was associated with poor gait function. Combining outcomes from these two studies, it appears that ongoing cortical reorganisation of the ipsilateral motor cortex following rehabilitation is associated with poor gait function. Both ICE and intracortical inhibition may be appropriate neurophysiological biomarkers of gait function in transtibial amputees.

In summary, three aspects of gait and mobility function in transtibial amputees were investigated. These findings expand current understanding of amputee gait and mobility and demonstrate the importance of investigating alternative assessments that may improve outcomes of clinical rehabilitation. The results of the work in this thesis have potential to improve understanding and knowledge of transtibial amputee rehabilitation and may inform future studies to improve outcomes of amputee rehabilitation.

PUBLICATIONS ARISING FROM THIS RESEARCH

Refereed manuscripts

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2014, 'Ipsilateral corticomotor excitability is associated with increased gait variability in unilateral transtibial amputees', *European Journal of Neuroscience,* vol. 40, no. 2, pp. 2454-62.

Hordacre, B, Barr, C & Crotty, M 2014, 'Use of an activity monitor and GPS device to assess community activity and participation in transtibial amputees', *Sensors,* vol. 14, no. 4, pp. 5845-59.

Hordacre, B & Bradnam, L 2013, 'Reorganisation of primary motor cortex in a transtibial amputee during rehabilitation: A case report', *Clinical Neurophysiology,* vol. 124, no. 9, pp. 1919-21.

Hordacre, B, Birks, V, Quinn, S, Barr, C, Patritti, BL & Crotty, M 2013, 'Physiotherapy rehabilitation for individuals with lower limb amputation: a 15-year clinical series', *Physiotherapy Research International,* vol. 18, no. 2, pp. 70-80.

Hordacre, BG, Stevermuer, T, Simmonds, F, Crotty, M & Eagar, K 2013, 'Lower-limb amputee rehabilitation in Australia: Analysis of a national data set 2004-10', *Australian Health Review,* vol. 37, no. 1, pp. 41-7.

Invited conference concurrent session presentations

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2013, 'Emerging Technologies In Amputee Rehabilitation: “What will the Future Look Like?”', paper presented to 2nd Singapore Rehabilitation Conference, Singapore.

Conference abstracts

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2014, 'Influence of the ipsilateral motor cortex on functional performance in unilateral transtibial amputees', paper presented to Australasian Military Medicine Association, Adelaide, Australia.

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2014, 'Reorganisation of the primary motor cortex in amputees undertaking prosthetic rehabilitation', paper presented to Australasian Neuroscience Society: Sensorimotor Satellite Meeting, Adelaide, Australia.

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2013, 'The relationship of ipsilateral and contralateral projections to the quadriceps on control of gait and balance in transtibial amputees', paper presented to Australasian Brain Stimulation Meeting, Melbourne, Australia.

Hordacre, B, Bradnam, L & Crotty, M 2013, 'Reorganisation of the primary motor cortex in amputees undertaking prosthetic rehabilitation', paper presented to Australasian Brain Stimulation Meeting, Melbourne, Australia.

Hordacre, B, Bradnam, L, Barr, C, Patritti, BL & Crotty, M 2012, 'Influence of the ipsilateral motor cortex on functional performance in unilateral transtibial amputees', paper presented to New Zealand Applied Neuroscience Conference, Auckland, New Zealand.

Hordacre, B, Birks, V, Quinn, S, Barr, C, Patritti, B & Crotty, M 2011, 'Changes in rehabilitation outcomes of lower limb amputees over 15 years: A clinical series', paper presented to Annual Scientific Meeting of ISPO Australia, Sydney, Australia.

Accepted conference abstracts

Hordacre, B, Barr, C & Crotty, M 2014, ‘Wearable technology to assess community activity and participation in transtibial amputees’, paper presented to 22nd Annual Scientific Meeting of the Australasian Faculty of Rehabilitation Medicine, Adelaide, Australia.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge I believe it does not contain any material previously published or written by another person except where due reference is made in the text.

The study in chapter three was conceived by myself and MC. I was responsible for applying for ethical approval. Data were obtained from the Australasian Rehabilitation Outcomes Centre (Wollongong, NSW). Data analyses were performed by myself under the guidance of TS. Interpretation of the data was completed by myself and MC. I was responsible for drafting the manuscript, and TS, FS, MC, KE reviewed the manuscript. The study in chapter four was conceived by myself, CB, BP and MC. I was responsible for applying for ethical approval. Data were collected by VB. I conducted data analyses under guidance from SQ. Interpretation of the data were completed by myself, CB, BP and MC. I was responsible for drafting the manuscript, and VB, SQ, CB, BP, MC reviewed the manuscript. The study in chapter five was conceived by myself and CB. I was responsible for applying for ethical approval, participant screening and recruitment, data collection, analysis and interpretation. I was responsible for drafting the manuscript, and CB, BP and MC reviewed the manuscript. The study in chapter six was conceived by myself and CB. I was responsible for applying for ethical approval, participant screening and recruitment, data collection and analysis. Interpretation of data was completed by myself and CB. I was responsible for drafting the manuscript, and CB, BP and MC reviewed the manuscript. The study in chapter seven was conceived by myself and

LB. I was responsible for applying for ethical approval, participant screening and recruitment, data collection and analysis. Interpretation of data was completed by myself and LB. I was responsible for drafting the manuscript, and LB, CB, BP and MC reviewed the manuscript. The study in chapter eight was conceived by myself and LB. I was responsible for applying for ethical approval, participant screening and recruitment, data collection and analysis. Interpretation of data was completed by myself and LB. I was responsible for drafting the manuscript, and LB and MC reviewed the manuscript.

I took a leadership role in preparing all manuscripts for submission to journals, and responding to reviewer comments. These responses were reviewed by all co-authors before re-submitting to the journals.

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across rehabilitation and control subjects.

LIST OF ABBREVIATIONS

50%MEP$_{MAX}$	Half Maximum Motor Evoked Potential
AMP-PRO	Amputee Mobility Predictor
AMT	Active Motor Threshold
ANOVA	Analysis of Variance
AN-SNAP	Australian National Sub-acute and Non-Acute Patient
AROC	Australasian Rehabilitation Outcomes Centre
CV	Coefficient of Variation
EMG	Electromyography
FIM	Functional Independence Measure
GABA	Gamma-Aminobutyric Acid
GPS	Global Positioning System
ICE	Index Corticospinal Excitability
ICF	Intracortical Facilitation
IHI	Interhemispheric Inhibition
IPP	Interim Prosthetic Program
IRR	Incidence Rate Ratio
ISP	Ipsilateral Silent Period
LI	Laterality Index
LICI	Long-latency Intracortical Inhibition
LOS	Length of Stay
M1	Primary Motor Cortex
M1$_{CON}$	Primary Motor Cortex Contralateral to the Amputated Limb
M1$_{IPSI}$	Primary Motor Cortex Ipsilateral to the Amputated Limb

MEP	Motor Evoked Potential
MEP_{MAX}	Maximal Motor Evoked Potential Response
MRI	Magnetic Resonance Imaging
rmsEMG	Root Mean Square Electromyography
NMDA	N-methyl-D-aspartate
NSW	New South Wales
OR	Odds Ratio
PVD	Peripheral Vascular Disease
Qld	Queensland
RF	Rectus Femoris
rmANOVA	Repeated Measures Analysis of Variance
RPD	Rehabilitation Program Duration
RRD	Removable Rigid Dressing
SA	South Australia
SAM	StepWatch3 Activity Monitor
SD	Standard Deviation
SICI	Short-latency Intracortical Inhibition
SR_{SLOPE}	Stimulus Response Curve Slope
TMS	Transcranial Magnetic Stimulation
Vic	Victoria

STRUCTURE OF THESIS

This thesis is divided into nine chapters. The first two chapters contain the introduction and literature review. Chapters three to eight contain studies that have either been published in peer review journals or are currently under review for publication. Each of these chapters contains an abstract, background, methods, results and discussion section related to that particular study. Chapter nine provides an overall discussion of the thesis.

Chapter one provides an introduction to the thesis, states the research questions and outlines the rationale for the thesis. The overall aim of this thesis is to investigate novel assessments of gait and mobility function in transtibial amputees. The research questions are;

- What outcomes are currently achieved by amputee rehabilitation units in Australia?
- Is the variability of speed normalised spatial-temporal gait parameters an important gait biomarker associated with falls history in transtibial amputees?
- Can wearable technology be used to assess community mobility function in transtibial amputees, and are measures of community mobility function associated with clinical assessments of normalised gait variability and falls history?
- Can TMS measures be used as neurophysiological biomarkers of gait function?

Chapter two summarises relevant literature for amputee prosthetic rehabilitation services and potential assessments of gait and mobility function. These assessments focus specifically on gait variability, wearable technology and neurophysiology of motor control.

Chapter three is titled ‘Lower-limb amputee rehabilitation in Australia: analysis of a national data set 2004-2010’. This chapter comprises a study which was published in *Australian Health Review*. The study identified that amputee rehabilitation units in Australia are facing challenges to ensure optimal rehabilitation outcomes.

Chapter four is titled ‘Physiotherapy rehabilitation for individuals with lower-limb amputation: A 15 year clinical series’ which was published in *Physiotherapy Research International*. This study identified challenges facing amputees in one Australian rehabilitation unit and how this has affected the functional outcomes they are able to achieve. This rehabilitation service was the site where participants were recruited for the subsequent experimental studies.

Chapter five is titled ‘Assessing gait variability in transtibial amputee fallers based on spatial-temporal gait parameters normalised for walking speed’ which is currently under review in *Gait and Posture*. This study demonstrated that normalised gait variability was greater in transtibial amputees with a history of falls, suggesting normalised gait variability may be an important measure of gait function.

Chapter six is titled ‘Use of an activity monitor and GPS device to assess community activity and participation in transtibial amputees’ which was published in the journal

Sensors. Participants in this study were selected from the same cohort studied in chapter five. This study demonstrated that gait function characterised by speed normalised gait variability was associated with different levels of community activity and participation.

Chapter seven is titled 'Ipsilateral corticomotor excitability is associated with increased gait variability in unilateral transtibial amputees' which was published in the *European Journal of Neuroscience*. Participants recruited for this study were a subset of those recruited for chapters five and six. This study identified a neurophysiological measure, the index of corticospinal excitability, which was associated with normalised gait variability. Therefore, the index of corticospinal excitability may be an appropriate biomarker of gait function in transtibial amputees.

Chapter eight is titled 'Reorganisation of the primary motor cortex following lower-limb amputation'. Part of this chapter was published in *Clinical Neurophysiology*. Participants in this study were recruited from the prosthetic rehabilitation facility described in chapter four. Thirteen participants completed neurophysiological assessments at key phases of rehabilitation using transcranial magnetic stimulation. Intracortical inhibition assessed at key phases of rehabilitation was predictive of normalised gait variability at discharge, and may be an appropriate biomarker of function in this population.

Chapter nine provides an overall discussion of the thesis and highlights the limitations and further research directions.

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Amputation of a lower-limb has a profound effect on gait and mobility function. Lower-limb prosthetic rehabilitation services aim to restore functional mobility through provision of a prosthesis, and extensive gait re-education. Accurate assessment of gait and mobility function is, therefore, of high importance to rehabilitation clinicians. While lower-limb amputee studies have predominantly investigated aspects of vascular interventions and prosthetic technology, few have specifically investigated alternative approaches to characterise gait and mobility function despite the importance of these outcomes in amputee rehabilitation. Alternative techniques to assess gait and mobility function currently used in other populations, such as people with neurological deficits, may provide important information for amputee rehabilitation. Current clinical assessments of amputee gait and mobility function have inherent limitations, restricting accuracy and reliability. The purpose of this thesis was to explore novel assessments of gait and mobility function in transtibial amputees.

1.1.1 Amputee rehabilitation service

Australian amputee rehabilitation facilities face an increase in demand for services due to an ageing population (Swan 2010) and increased survival of people with comorbidities. For example a rising prevalence of adult onset diabetes (Becker et al. 2011; Varu, Hogg & Kibbe 2010) may lead to increased rates of major limb amputation (Carmona et al. 2005). The presence of comorbidities may also slow recovery and extend time in rehabilitation. There is currently limited understanding of how age and comorbidities have affected amputee rehabilitation outcomes at the

service level. Prior to investigating new assessments of gait and mobility function, it is important to establish the current state of Australian amputee rehabilitation. Most Australian rehabilitation services contribute to the Australasian Rehabilitation Outcomes Centre (http://ahsri.uow.edu.au/aroc/index.html) to allow benchmarking of rehabilitation outcomes. Accessing this dataset provides insight into current amputee presentations and outcomes. In addition, accessing one hospital service dataset monitored over a 15 year period allows an overview of changes in clinical characteristics and rehabilitation outcomes over time. Examination of contemporary amputee rehabilitation services will highlight current challenges for clinical services to successfully restore gait and mobility function in lower-limb amputees and identify priority areas for research or opportunities to improve clinical practice.

1.1.2 Characterising gait and mobility function

Assessments of gait and mobility function have traditionally relied upon either subjective (e.g. questionnaires) or objective (e.g. timed walk tests) measures. New assessments to characterise gait and mobility function in transtibial amputees may progress understanding and lead to investigation of new interventions to improve functional outcomes. Currently, little evidence is available on interventions to improve gait and mobility function in this important group and this should be addressed. However, prior to investigating potential interventions that aim to improve function it is important to characterise new aspects of gait and mobility to assist identification of potential interventions which may be beneficial. Contemporary functional assessments have successfully been implemented in the clinical setting to support rehabilitation of various pathological conditions. For example, quantitative gait analysis of older adults was able to identify clinical

measures predictive of falls risk (Verghese et al. 2009), while in stroke neurophysiological assessments such as transcranial magnetic stimulation and functional magnetic resonance imaging may assist rehabilitation by predicting functional recovery (Stinear et al. 2012). Amputee rehabilitation may likewise benefit, and should consider new ways to assess, characterise and understand gait and mobility function. Possible benefits include improved knowledge of amputee gait and mobility function, greater efficiency of clinical practice and potentially improved patient outcomes following identification of effective interventions to improve function. These benefits may assist specific challenges faced by amputee rehabilitation units identified in this thesis.

While there are many potential gait and mobility function assessments which have relevance for amputee rehabilitation, studies in this thesis sought to investigate three specific areas of gait and mobility function. These were; spatial-temporal gait variability, community mobility via wearable technology and neurophysiological biomarkers of gait function using transcranial magnetic stimulation.

1.1.2.1 Gait variability to assess function

Computerised walkways or motion capture systems allow accurate quantitative assessment of spatial-temporal gait parameters which provide clinicians with an additional tool to assess gait function. Gait variability is an objective measure which quantifies fluctuations of spatial-temporal gait parameters. It is considered a sensitive measure of gait dynamics, with increased gait variability associated with falls in a range of pathological populations including amputees (Grimbergen et al. 2008; Lord et al. 2011b; Parker, Hanada & Adderson 2013; Sheridan et al. 2003; Socie et al.

2013; Vanicek et al. 2009; Verghese et al. 2009). Prosthetic gait is complex and challenging for amputees to master. Many amputees experience a fall (Miller, Speechley & Deathe 2001; Pauley, Devlin & Heslin 2006). Therefore, sensitive measures of gait function that are associated with falls may be important for amputee clinical practice. Further investigation of the assessment and application of spatial-temporal gait variability as a measure of gait function is warranted.

1.1.2.2 Wearable technology to assess community function

Achieving adequate levels of community mobility function is important following prosthetic rehabilitation, however a high proportion of amputees fail to achieve this (Van Velzen et al. 2006). Clinical gait assessments associated with community mobility function are important for amputee rehabilitation, and gait variability may be an appropriate measure. To further understand the clinical significance of gait variability measures, the relationship of these descriptors with function in the community should be investigated. Advances in wearable technology offer a means to better assess mobility function in the community. Small and portable devices are worn on a person to record activity, physiological or biological data (Bonato 2010; Teng et al. 2008). With improved technology, battery life and data storage capacity these devices are now capable of recording data in home or community setting for both diagnostic or monitoring applications (Bonato 2005). Wearable technology may improve assessment of mobility function in transtibial amputees, and may prove superior to current subjective and objective assessments which have limitations of accuracy and reliability (Corrigan & McBurney 2008; Grise, Gauthier-Gagnon & Martineau 1993; Smith, Brown & Ubel 2008; Stepien et al. 2007). Assessment of

community activity and participation with wearable technology may confirm there is a relationship between gait variability and community integration.

1.1.2.3 Neurophysiological biomarkers of function

In humans, understanding neurophysiology of motor control has provided insight into the execution and control of movement. Amputation of a limb results in reorganisation of the motor cortex (Cohen et al. 1991; Donoghue & Sanes 1988; Fuhr et al. 1992; Sanes et al. 1988), and it is probable that gait function will be altered secondary to this. Further, prosthetic rehabilitation requires amputees to learn to move in a new way. Clinical therapists spend significant time training motor control and gait patterns of patients with functional movement disorders using interventions targeted at improving control and execution of movement (Shumway-Cook 2012). However, relatively little attention has been given to the well-established principles of motor learning and motor control in the amputee population to enable amputees to achieve safe prosthetic mobility and independence (Sawers et al. 2012).

For other pathologies requiring rehabilitation, understanding neurophysiology and motor control has allowed identification of biomarkers associated with potential for functional recovery. Stroke is one neurological condition where a significant amount of research has been dedicated to understanding the cortical correlates of injury and recovery (Grefkes & Fink 2011; Hallett 2001; Murase et al. 2004; Shimizu et al. 2002; Stinear 2010; Stinear et al. 2012; Stinear et al. 2007; Ward et al. 2006). Knowledge of neurophysiology and motor cortex reorganisation after stroke has resulted in research and development of new interventions to improve functional

outcomes (Bolognini, Pascual-Leone & Fregni 2009; Byblow et al. 2012; Hummel & Cohen 2006; Rogers et al. 2011; Schlaug, Marchina & Wan 2011; Schulz, Gerloff & Hummel 2013). Similar identification of neurophysiological biomarkers in transtibial amputees would improve understanding of the neurophysiology of gait function and control over rehabilitation. This knowledge would have the potential to improve functional outcomes and guide future interventional studies by identifying patterns of cortical reorganisation associated with poor gait function and applying targeted interventions to drive optimal patterns of cortical reorganisation to achieve better function. The ability to improve amputee gait function by reducing gait variability, thereby improving gait function, may have significant implications for amputee rehabilitation. Further investigation of neurophysiology and gait function in transtibial amputees is warranted.

1.2 Research Objectives

In order to examine challenges to restoring mobility following amputation, novel assessments of gait and mobility function were investigated. Several research objectives for this thesis have been identified. They are:

- To describe patterns of amputee rehabilitation in Australia.
- To characterise a descriptor of gait, specifically the variability of speed normalised spatial-temporal gait parameters, and assess its potential utility as a marker of falls in amputees.
- To investigate the feasibility of wearable technology for assessment of community mobility function in transtibial amputees, and determine the

relationship between community mobility and clinical assessments of gait function and falls history.

- To identify potential neurophysiological biomarkers of gait function using transcranial magnetic stimulation in transtibial amputees.

CHAPTER TWO: LITERATURE REVIEW

2.1 Amputation

Amputation is the removal of all or part of a limb or peripheral extremity from the body. The level of amputation has important ramifications for function, and is described by the bone or joint transected. Common levels of lower-limb amputation include transfemoral (above knee), knee disarticulation (through knee), transtibial (below knee) and ankle disarticulation (though ankle). Causes for amputation include trauma, congenital deformities and medical reasons (e.g. malignancy, vascular complications, or infection). Restoration of gait and mobility function can be influenced by these factors (Davies & Datta 2003; Genin et al. 2008; Sansam et al. 2009), demonstrating the complexities of amputee rehabilitation.

2.1.1 Etiology of lower-limb amputation

Lower-limb amputees in the developed world are often elderly patients presenting with peripheral vascular disease and type II diabetes mellitus. Non-vascular presentations such as malignancy, trauma or infection represent approximately 15% of amputee episodes in rehabilitation units (Nehler et al. 2003; Pernot et al. 2000; Stone et al. 2007; Wu, Chan & Bowring 2010). Peripheral vascular disease is a medical presentation where blood flow in peripheral arteries is obstructed due to narrowing of the lumen. The result is reduced circulation. Narrowing of the lumen, or internal structure of the artery, is typically caused by an atherosclerotic process due to an excessive inflammatory and fibroproliferative response to numerous vascular insults (Dieter et al. 2002). Chronic inflammation within the blood vessel leads to an increased number of macrophages and lymphocytes causing alteration to the normal homeostatic properties of the endothelium; the thin layer of cells which

line the interior surface of blood vessels (Dieter et al. 2002; Ross 1999). Eventually the artery can no longer compensate by dilation, resulting in a narrowing of the artery and restricted blood flow (Ross 1999). Symptoms may include claudication (pain, weakness or loss of sensation in the limb), slow healing of wounds or ulcers, altered colour or temperature of the limb and reduced hair and nail growth (Gornik & Beckman 2005; Ouriel 2001). With disease progression, severity of pain increases and may occur not only with activity, but also at rest (Ouriel 2001). Amputation of the limb is often performed when revascularisation surgical procedures and lifestyle modifications have failed (Gornik & Beckman 2005; Luther et al. 1996; Ouriel 2001). In these instances, the aim is to relieve pain and prevent further vascular complications.

The presence of diabetes mellitus accelerates the progress of peripheral vascular disease (Haffner et al. 1998; Stump, Clark & Sowers 2005). It is suggested that this is due to metabolic consequences associated with hyperglycaemia, endothelial dysfunction, inflammation or the coexisting condition of hypertension (Cernes, Zimlichman & Shargorodsky 2008; Chen et al. 2011; Fox et al. 2007; Handelsman 2011; Winer & Sowers 2007). Globally 366 million people were diagnosed with diabetes in 2011, and this figure is expected to increase to 552 million by 2030 (Guariguata et al. 2014). In Australia, type II diabetes mellitus is the fastest growing chronic disease, with an increase of approximately 8% per year since 2000 (Australian Institute of Health and Welfare 2008). Peripheral vascular disease and diabetes may delay recovery from amputation and restoration of functional prosthetic mobility. Ongoing management of vascular, renal and diabetic comorbidities along

with constant wound care and monitoring of the remaining limb all contribute to vascular amputees being a major public health concern.

2.2 Challenges Facing Amputee Rehabilitation Services

The aim of amputee rehabilitation is to restore gait and mobility function (Sansam et al. 2009) and facilitate successful re-integration to community living. Complexities of common lower-limb amputee presentations, such as multiple comorbidities and advanced age, may contribute to significant variation in rehabilitation outcomes, and the ability to restore gait and mobility function. Older age and a high number of comorbidities in amputees admitted for rehabilitation have been shown to reduce the likelihood of achieving prosthetic mobility and independent living following amputation (Bhangu, Devlin & Pauley 2009; Fletcher et al. 2002; Kurichi et al. 2007; Lim et al. 2006; Schoppen et al. 2003). In addition, the common comorbidity of peripheral vascular disease may further contribute to difficulties in achieving gait and mobility function following lower-limb amputation. A significant proportion of vascular amputees do not use their prosthesis following rehabilitation (Bhangu, Devlin & Pauley 2009; McWhinnie et al. 1994; Schoppen et al. 2003; Wolf et al. 1989). Cardiac disease is also prevalent in around 75% of vascular amputees (Erjavec, Prešern-Štrukelj & Burger 2008; Moore et al. 1989) and has potential to greatly limit prosthetic mobility due to the increased energy expenditure associated with prosthetic mobility. Vascular disease associated with the primary amputation may contribute to bilateral amputations at a later stage, as the disease will likely affect both limbs. Following the initial amputation, there is a 33-50% risk of a second lower-limb amputation occurring within 5 years (Dawson 1995; Kerstein et

al. 1975). Functional gait and mobility would be adversely affected following bilateral amputation. In addition, vascular amputees have high mortality rates ranging from 16-56% two years after amputation (Gugulakis et al. 1999; Pohjolainen, Alaranta & Wikstrom 1989). Maintaining a level of mobility in these amputees may assist in reducing these mortality rates as loss of mobility has been associated with increased mortality rates in older adults (Hardy et al. 2007; Hirvensalo, Rantanen & Heikkinen 2000; Studenski et al. 2011).

Despite these additional difficulties in rehabilitating vascular amputees, this group is often underrepresented in amputee research (Fortington et al. 2012), potentially due to increased mortality rates and comorbidities making participant recruitment difficult (Gugulakis et al. 1999; Pohjolainen, Alaranta & Wikstrom 1989). Restoration of gait and mobility function is an important rehabilitation goal for these amputees. Amputee rehabilitation facilities must consider the potential success of achieving prosthetic mobility in this cohort of amputees which are commonly found in Australian rehabilitation facilities.

2.2.1 How can these challenges be addressed?

Although age and comorbidities may present challenges in successfully restoring gait and mobility function, it is unclear how this has affected outcomes of current amputee rehabilitation services. Therefore, it is important to establish if complex amputee presentations do in fact impose difficulties in optimising gait and mobility function during rehabilitation. If this is established, investigation of new functional assessments may identify more accurate measures that better detect problems, assist clinical decisions and improve rehabilitation outcomes. Functional assessments are

important outcome measures in establishing evidenced-based practice (Garratt et al. 2002; Stevens et al. 2001). Therefore, investigation of novel assessments of gait and mobility function are important to progress understanding and knowledge of amputee rehabilitation. This thesis will seek to characterise gait and mobility function using new approaches to provide a different perspective on this important outcome.

2.3 Scope of Thesis

This thesis will firstly investigate the current state of amputee rehabilitation in Australia. Reviewing contemporary amputee prosthetic rehabilitation services will highlight the requirements for further amputee rehabilitation research to be conducted. Following the review of amputee prosthetic rehabilitation service provision, three new assessments of gait and mobility function will be explored. It is envisaged these assessments of function will serve to provide further understanding of amputee gait and mobility function to that provided by current clinical assessments. As amputee presentations are complex with many different factors affecting gait and mobility function (Davies & Datta 2003; Gauthier-Gagnon, Grisé & Potvin 1998; Geertzen et al. 2005; Hermodsson, Ekdahl & Persson 1998; Taylor et al. 2005), the new assessments investigated will specifically focus on transtibial amputees in order to eliminate the influence that level of amputation may have on gait and mobility outcomes. Transtibial amputees were selected as they are the most common group of amputees found in rehabilitation units (Lim et al. 2006; Wu, Chan & Bowring 2010).

There are many potential novel assessments of function which may assist characterisation of amputee gait and mobility function. This thesis sought to investigate a few selected assessments. First, a high proportion of amputees experience falls (Miller, Speechley & Deathe 2001). Therefore measures of gait function associated with falls have importance for amputee rehabilitation. Spatial-temporal gait variability has been associated with falls for a range of pathologies (Grimbergen et al. 2008; Lord et al. 2011b; Sheridan et al. 2003; Socie et al. 2013; Verghese et al. 2009), including lower-limb amputees (Parker, Hanada & Adderson 2013; Vanicek et al. 2009). However protocols to assess gait variability can be improved (König et al. 2014), including procedures to normalise for variations in walking speed. Speed normalised gait variability may not only be associated with falls, but also community integration. Fear of falls is known to reduced mobility and social activity (Howland et al. 1998; Tinetti et al. 1994b; Vellas et al. 1997), limiting the capacity of the amputee to reintegrate into the community. Therefore it is likely that measures of community activity and participation are associated with gait variability measures. Wearable technology is a novel method to enhance assessment of community integration by monitoring activity and participation within the community and may be appropriate as a clinical assessment of mobility. Finally, many factors affect gait variability, and one of these factors, altered motor control, will be investigated to identify potential neurophysiological biomarkers of function. Lower-limb amputation is associated with reorganisation of the motor system (Chen et al. 1998a; Fuhr et al. 1992). Therefore it is likely that motor control may be altered. Understanding the relationship between reorganisation of the motor system and gait function may allow identification of potential neurophysiological biomarkers. Investigation of biomarkers may assist clinical practice by identifying

amputees requiring further intervention to improve functional outcomes. It may also progress understanding of amputee motor control and identify potential treatment techniques to improve gait function in future studies. The current literature on amputee rehabilitation services, gait variability, wearable technology and motor control will now be reviewed.

2.4 Amputee Rehabilitation Services in Australia

Amputee rehabilitation services typically employ a multidisciplinary approach to achieve optimum levels of physical, mental, emotional, social, and vocational status (Geertzen, Martina & Rietman 2001). Often the primary aim of prosthetic rehabilitation is to restore a functional level of mobility (Sansam et al. 2009). While mental, emotional, social and vocational levels may improve as a result of achieving prosthetic mobility, it still remains important for amputee rehabilitation services to monitor these aspects (Fleury, Salih & Peel 2013; Sansam et al. 2009; Schoppen et al. 2003). One of the challenges for amputee rehabilitation services is to determine suitability for prosthetic mobility. In some instances the provision of a wheelchair and prosthesis for transfers may be the most appropriate mobility option (Pell et al. 1993). Where a prosthesis is provided for mobility, clinicians must determine the most appropriate prosthetic equipment. To successfully achieve this, a number of factors must be considered which include, medical comorbidities and conditions, age, physical requirements, employment status, amputation level and stump length (Fleury, Salih & Peel 2013; Kurichi et al. 2007; Van Der Linde et al. 2004a; Wolf et al. 1989). Upon provision of a prosthesis, extensive prosthetic rehabilitation is initiated. Prosthetic rehabilitation aims to improve mobility endurance, strength,

balance and educate the patient regarding prosthetic use (e.g. don/doff prosthesis) and skin care (Coletta 2000; Miklos 2007). However, ageing of the population and improved survival of people with chronic disease has led to dangers in prosthetic rehabilitation. For instance, the prevalence of comorbidities amongst amputees my not only affect pre-amputation mobility, a factor known to affect post-amputation prosthetic mobility (Taylor et al. 2005), but may also reduce physical capacity to achieve optimal levels of mobility with a prosthesis (Johnson, Kondziela & Gottschalk 1995; Sansam et al. 2009). Vascular comorbidities may also delay wound healing (Ten Duis et al. 2009), leading to rehabilitation delays or program interruptions. In addition, vascular and diabetic comorbidities contributing to the initial amputation may lead to subsequent revisions to higher levels, or amputation of the other lower-limb (Dawson 1995; Kerstein et al. 1975). The advanced age of many amputees in rehabilitation may affect prosthetic use. In one study, less than 75% of elderly amputees initially provided with a prosthesis for mobility were using it shortly following rehabilitation (Steinberg, Sunwoo & Roettger 1985). Age of amputees in rehabilitation is likely to continue to increase in the future (Fletcher et al. 2002), suggesting this confounder to achieving optimal gait function will continue to cause difficulty. These factors are a concern for prosthetic rehabilitation facilities, so identification of those likely to benefit from a prosthesis would be useful for clinical practice.

2.4.1 Review of prosthetic rehabilitation outcomes

It is currently unclear how complexities of amputee presentations affect rehabilitation outcomes. For Australian amputee rehabilitation facilities, there are a limited number of studies reviewing demographics, clinical characteristics and

functional outcomes (Hubbard 1989; Jones 1990b; Jones, Hall & Schuld 1993; Katrak & Baggott 1980; Lim et al. 2006; Wu, Chan & Bowring 2010). Of the identified studies, only two were published within the last 10 years (Lim et al. 2006; Wu, Chan & Bowring 2010). The earlier of these studies reviewed lower-limb amputee episodes from one hospital service between 2000 and 2002. A total of 87 episodes were included in the analysis which identified that amputees were primarily male, presenting with multiple comorbidities. Peripheral vascular disease was the most common reason for amputation in these elderly amputees (mean age 70 years). Only 45% of amputees were identified as having rehabilitation potential. Of those, approximately 80% used a prosthesis for indoor and outdoor mobility. The latter of these studies identified similar trends of gender, age and comorbidities from a single hospital service between 1994 and 2006. However, a higher proportion of amputees were admitted to rehabilitation (71%) which may reflect differences in admission criteria between these two rehabilitation services. It is interesting that contemporary reviews of Australian amputee rehabilitation services were not identified in this review. Given that the most recent data are now eight years old, it is necessary to further investigate more recent trends in amputee rehabilitation services. Identifying difficulties and issues for rehabilitation services from more contemporary rehabilitation data would provide a context to the further studies comprised in this thesis.

2.5 Spatial-Temporal Gait Variability to Assess Gait Function

Gait variability is an objective measure of gait function which has been associated with falls in older adults and various pathological conditions. Clinical assessments of

gait function are required to further understand amputee gait and interpret falls risk in transtibial amputees.

2.5.1 Gait variability

In healthy adults, the locomotor system integrates inputs from the primary motor cortex (M1), cerebellum and basal ganglia, with addition of feedback from the visual, vestibular and proprioceptive systems producing motor commands to execute coordinated muscle firing and limb movement (Hausdorff 2007). The result is a highly consistent walking pattern with little variation in spatial-temporal gait parameters from stride-to-stride. Spatial gait parameters are length measures and include step-length, step-width, and stride-length. Temporal gait parameters are time based measures and include step-time and stride-time.

There has been growing interest in the fluctuation of these parameters from stride-to-stride. In addition to mean spatial-temporal measures, the standard deviation or coefficient of variation can be used to describe variability of stride-to-stride gait parameters. Gait variability is believed to reflect the underlying motor control of gait and is sensitive to different pathological or ageing conditions (Hausdorff 2007). Recently, gait variability was found to differentiate older adults with mobility and cognitive impairment, and predict those with future cognitive decline (Verghese et al. 2007). Further, gait variability was greater in those with history of falls for a range of populations including lower-limb amputees (Parker, Hanada & Adderson 2013; Vanicek et al. 2009), older adults (Hausdorff, Rios & Edelberg 2001; Verghese et al. 2009), people with multiple sclerosis (Crenshaw et al. 2006; Socie et al. 2013), Parkinson's disease (Hausdorff et al. 1998; Lord et al. 2011a), Huntington's disease

(Grimbergen et al. 2008) and Alzheimer's disease (Sheridan et al. 2003). Therefore assessment of gait variability has the potential to be a sensitive objective measure of gait function in rehabilitation.

2.5.2 Falls

For rehabilitation, falls assessment is an important focus. Sensitive measures to predict falls risk or discriminate falls history have substantial value given the negative consequences and significant cost on the health care system associated with falls (Stevens et al. 2006; Tinetti & Williams 1997). Intrinsic risk factors for falls include age, chronic disease, gait and balance instability, decreased vision, altered mental status and medication use (Sattin 1992). Many, if not all, of these factors would likely be prevalent in the elderly vascular amputees found in amputee rehabilitation facilities. In addition, the physical loss of plantar flexor musculature, reduced muscle strength of the quadriceps and mechanical limitations of prosthetic feet componentry predispose transtibial amputees to an altered gait pattern and increased risk of falls (Miller, Speechley & Deathe 2001).

Evidence of falls is well documented in lower-limb amputees with over 50% of community based amputees reporting a fall in the previous 12 months (Miller, Speechley & Deathe 2001). Approximately 17-30% of lower-limb amputees experience a fall in rehabilitation (Dyer et al. 2008; Gooday & Hunter 2004; Pauley, Devlin & Heslin 2006; Yu et al. 2010) with half resulting in some form of injury to the individual (Gooday & Hunter 2004) leading to a longer hospital stay (Yu et al. 2010). Experiencing a fall has been associated with functional limitations, decline in independence, reduced confidence and self-imposed restriction of activity (Kulkarni

et al. 1996; Tinetti et al. 1994b). Fear of falling is also common in amputees (Miller, Speechley & Deathe 2001), and is associated with reduced mobility and social activity (Howland et al. 1998; Tinetti et al. 1994b; Vellas et al. 1997). The activity limitations and participation restrictions associated with falls history or fear of falls highlight the importance of identifying sensitive measures of gait function, such as gait variability, associated with falls. Discriminatory measures to identify falls risk have significant value in this population and should be investigated.

2.5.3 Test protocols for gait variability

Spatial-temporal gait variability can be assessed using a number of gait analysis techniques including repeated walk trials across a computerised walkway (Lord et al. 2011b), motion capture systems (Vanicek et al. 2009), gyroscopes (Najafi et al. 2009) or tri-axial accelerometers (Hartmann et al. 2009a; Paterson, Hill & Lythgo 2011). For computerised walkways and motion capture systems, test protocols include repeated walks over a data capture area to achieve a high number of strides to accurately assess gait variability. A wide range of test protocols, variability parameters, and calculations of gait variability have been reported (Lord et al. 2011b). While many studies have investigated aspects of gait variability and its potential use in rehabilitation, further clarification of test protocols may be required. A recent review suggested future studies should report both standard deviation and coefficient of variation as measures to quantify gait variability, and ensure a minimum of 12 steps are collected to improve reliability of data (Lord et al. 2011b). However, earlier studies recommended data be collected over a greater number of steps, up to 120, to reliably measure variability (Hartmann et al. 2009a; Hollman et al. 2010). Consideration should be given to the patient population to ensure that

fatigue induced by the desire for high step counts does not affect the measure of gait variability (Cortes, Onate & Morrison 2014).

Gait variability measured from short interrupted walks is higher than continuous walk test protocols (Paterson, Lythgo & Hill 2009). While many studies use both test protocols, it is generally considered that continuous walking may be more accurate. Greater accuracy is likely to be due to reduced intra-subject variation in gait speed by allowing spatial-temporal rhythms to become established (Lord et al. 2011b). For an individual subject, variation in gait speed between individual walk trials is a potential confounder of gait variability findings (Beauchet et al. 2009; Helbostad & Moe-Nilssen 2003; Kang & Dingwell 2008). While previous work has investigated speed normalisation of gait parameters in adults walking at a range of speeds (Helbostad & Moe-Nilssen 2003; Van Iersel, Olde Rikkert & Borm 2007), these techniques have not been implemented in studies using interrupted walks to assess gait variability in patient populations. This may be especially important given difficulties various pathological groups have with mobility, and should be a technical consideration in the analysis of gait variability.

2.5.4 Gait variability in lower-limb amputees

Limited literature exists for amputee gait analysis and falls, with some suggestion that gait variability may be greater in transtibial amputees with a history of falls. Fallers were found to have greater amputated limb swing-time variability (Vanicek et al. 2009), and non-amputated limb step-time variability (Parker, Hanada & Adderson 2013). While both studies reported variability over a reasonable number of strides, sample sizes were small (n = 11 and n = 34 respectively) making it difficult to be

conclusive about these findings. In one study, there was an attempt to statistically control for speed and balance confidence. When analysed in this manner, gait variability was no longer significantly greater in those transtibial amputees with a history of falls (Parker, Hanada & Adderson 2013). Statistically controlling for speed as a covariate raises two methodological concerns. Firstly, as acknowledged by the authors, the relatively small sample size may have contributed to their inability to report a significant finding. Secondly, the methodology employed to control for gait speed would only control for the difference in gait speed between the faller and non-faller groups which may be an important variable to consider (Astephen Wilson 2012). Controlling for gait speed in this manner would remove the effect of gait speed from speed dependent parameters, and it is therefore not surprising that a non-significant finding was made (Astephen Wilson 2012). However, controlling for intra-subject gait speed variability is a different, but important methodological factor where repeated walk trials are performed. Intra-subject speed variability may result in inaccurate assessment of spatial-temporal gait variability. Variation in intra-subject speed across individual trials has been demonstrated to increase gait variability (Beauchet et al. 2009; Helbostad & Moe-Nilssen 2003; Kang & Dingwell 2008). Therefore, controlling for intra-subject gait speed variability should be considered.

Transtibial amputee gait variability studies identified in this review utilised protocols that require repeated walk trials at the participants comfortable gait speed (Parker, Hanada & Adderson 2013; Vanicek et al. 2009). One study required participants to complete 12 walk trials over a 10 meter walkway (Vanicek et al. 2009), while the other had participants complete 8 walk trials over a 6.1 meter walkway (Parker,

Hanada & Adderson 2013). Neither study reported if variability in gait speed occurred between individual trials. As amputee gait is associated with decreased endurance and increased energy cost of walking (Gailey et al. 1994; Genin et al. 2008; Sansam et al. 2009; Schmalz, Blumentritt & Jarasch 2002; Waters et al. 1976), it is possible that gait speed may vary between trials in this population. Therefore analysis of gait variability should consider methodology to control for this and improve quality of the analysis.

The apparent lack of stringent scientific studies investigating gait variability and falls in amputees is surprising. Given the significance of falls in amputees and the importance of gait variability as a marker in other conditions, gait variability is a measure which requires investigation. The literature suggests that studies investigating gait variability and falls should consider gait speed normalisation as a methodological technique and this thesis investigated this approach.

2.6 Wearable Technology to Assess Community Mobility

Wearable technology may be an important technology advancement in the field of rehabilitation, and in particular may assist the analysis of mobility. Instruments are capable of recording objective data from small portable devices worn or attached to the person of interest (Bonato 2010; Teng et al. 2008). Data may be recorded in the device for a period of time, or alternatively, linked via wireless networks to provide real-time data analysis. Ability to remotely monitor activity can provide rehabilitation clinicians with accurate objective data, otherwise unobtainable and difficult to replicate in a clinic setting.

Assessment of mobility function may be performed by many devices including global positioning system (GPS) devices and accelerometer based step count monitors. It was suggested that GPS devices are able to assess human location (Schutz & Chambaz 1997), and in combination with accelerometers, could assess activity and participation in the community. Activity and participation is an important domain of the International Classification of Functioning, Disability and Health (WHO 2001, 2002). The ability to accurately and objectively measure physical activity and community participation would provide important knowledge of mobility function in amputees, assisting rehabilitation clinicians. To date, this approach has not been assessed in transtibial amputees.

2.6.1 Activity and participation

In 2001, the World Health Assembly introduced the International Classification of Functioning, Disability and Health which is now considered a globally accepted framework and classification system to describe, assess and compare function and disability (WHO 2001, 2002). The International Classification of Functioning, Disability and Health framework is based on an integrated biopsychosocial model of human function and disability and can enhance understanding of interactions between people and the environment, activities and participation (Üstün et al. 2003). The International Classification of Functioning, Disability and Health provides a holistic approach to describe various health conditions, identify appropriate assessments and implement appropriate evidenced based interventions aimed at maximising health related outcomes. To help translate the International Classification of Functioning, Disability and Health into clinical practice and

research, ‘Core Sets’ focussing on specific disabilities have been developed (Kohler et al. 2009).

In 2011, a review of 113 amputee (general and specific) outcome measures was conducted (Xu, Kohler & Dickson 2011). Concepts of these assessments were linked to the key domains of the International Classification of Functioning, Disability and Health. The identified concepts were linked to a total of 130 categories in the domains of body function and structure, activities and participation and environmental factors. The 130 categories identified in this review will assist future development of amputee specific International Classification of Functioning, Disability and Health Core Sets. The majority of concepts were linked to the domain of activity and participation, potentially demonstrating the significance of these outcomes for amputee rehabilitation. In 2009, a review was conducted into outcome measurements that assess the activity domain in lower-limb amputees (Deathe et al. 2009). A total of 17 clinical objective and subjective assessments were identified, all of which addressed aspects of activity. These assessment tools were categorised as walk tests, mobility grading tools or indices of function. The authors identified that while the reviewed instruments were potentially important in the assessment of activity, most instruments require further investigation to demonstrate they are reliable assessments of activity. Activity limitation is a key domain for describing function, disability and health in patient populations. Therefore, accurate and reliable assessments are important for rehabilitation.

2.6.2 Current assessment of activity and participation

Subjective and objective assessments are currently used to assess activity and participation in the community following rehabilitation. Both forms of assessments have advantages and disadvantages in terms of reliability and validity. Firstly, subjective assessments of community activity were found to be unreliable in lower-limb amputees (Bussmann, Grootscholten & Stam 2004; Stepien et al. 2007). Subjective assessments can be influenced by both the subject and the examiner limiting the reliability of data (Bussmann & Stam 1998). Despite this, a range of self-reported assessments of activity and participation are widely used in amputee clinical practice and research applications due to their ease of administration (Deathe et al. 2009). Similarly, objective clinical measures are also widely used to assess community activity and participation in amputees. There are a range of tools in clinical practice including timed walk tests (e.g. six minute walk test, ten meter walk test) and mobility grading systems (e.g. special interest group in amputee medicine mobility grades, K level classification). A common tool to assess mobility potential of amputees is the amputee mobility predictor (AMP-PRO) (Gailey et al. 2002). Scores from the AMP-PRO guide categorisation of amputees into 5 functional levels describing community ambulation potential (K level classification, see figure 2.1 for description) (Health Care Financing Administration 2001). The five K level categories are used to determine prescription of prosthetic componentry. Provision of prosthetic componentry should reflect mobility requirements of the amputee. While the AMP-PRO was originally found to be highly correlated to the six minute walk test (Gailey et al. 2002), it is unknown whether the AMP-PRO accurately predicts community activity and participation. This is despite the AMP-PRO being used to guide K level categorisation and prescribe prosthetic componentry.

In addition to the AMP-PRO, objective timed walk assessments are often used to assess activity potential. Moderate correlations have been reported between self-reported measures of community ambulation performance and both the timed-up-and-go test ($r = 0.50 – 0.64$) and the two minute walk test ($r = 0.50 – 0.64$) (Miller, Deathe & Speechley 2001). This finding indicates that the timed-up-and-go and two minute walk test may be used to indicate community activity. However these results should be considered conservatively given the relative inaccuracies of self-reported measures used to determine community activity levels in this study. More recently, the two minute walk test has been identified as a measure which is highly correlated with daily step counts objectively assessed in the community with an accelerometer (Parker et al. 2010). The association of the two minute walk test with an accurate, objective assessment of community activity is potentially a greater indication of the association with community activity. However, a limitation of an activity monitor to assess step counts is that contextual factors such as where this activity occurred (at home or in the community) and levels of participation are missing in order to further describe key domains of the International Classification of Functioning, Disability and Health model. While the relationship between clinical assessments and community activity is important, further characterisation of community mobility should be considered to provide a more comprehensive understanding of activity and participation for lower-limb amputees.

K0	Does not have the ability or potential to ambulate or transfer safely with or without assistance, and a prosthesis does not enhance quality of life or mobility
K1	Has ability or potential to use a prosthesis for transfers or ambulation in level surfaces at a fixed cadence. Typical of the limited or unlimited household ambulator
K2	Has ability or potential for ambulation with the ability to transverse low-level environmental barriers such as curbs, stairs, or uneven surfaces. Typical of the limited community ambulator
K3	Has ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to transverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic use beyond simple locomotion
K4	Has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete

Figure 2.1: The K level classification systems for amputees

Another common objective timed walk test often associated with activity and mobility is gait speed. Studies in stroke survivors often use gait speed as a measure to differentiate community ambulation abilities. A gait speed of 0.8 m/s is typically proposed as the threshold required for full community ambulation, with 0.4 - 0.8 m/s indicating limited community ambulation and < 0.4 m/s indicating household ambulation (Jorgensen et al. 1995; Lord et al. 2004; Perry et al. 1995). However, concerns have been raised over the use of timed ambulation clinical measures to solely identify community ambulation levels. First, gait speed assessed in the clinic is not an accurate reflection of gait speed in the community (Taylor et al. 2006). Second, ambulation velocities and distances required for safe community ambulation vary dramatically depending on environmental factors (Robinett & Vondran 1988). Additionally, there are differences in mobility requirements in controlled

environments and in the community (Lord et al. 2005; Patla & Shumway-Cook 1999; Robinett & Vondran 1988). While the gait speed of 0.8m/s is suggested to indicate full community ambulation after stroke, this figure has been used in non-stroke populations, such as incomplete spinal cord injury (Behrman et al. 2005) and older adults (Plummer-D'Amato, Altmann & Reilly 2011) without validation for these populations. Translation of this measure to lower-limb amputees would appear inappropriate as clinically assessed amputee gait speed is typically greater than 0.8m/s (Vanicek et al. 2009) despite many not achieving full community ambulation (Van Velzen et al. 2006). Therefore this measure may not be suitable for lower-limb amputees.

In summary, a limitation of objective clinical assessments is that they fail to replicate the range of physical demands and unpredictable nature of community ambulation and participation (Corrigan & McBurney 2008). Therefore, objective measures may not accurately reflect true abilities of community activity and participation. Although associations were found between activity measures (step counts) and the two minute walk test, the domain of participation was not addressed despite its significance to the International Classification of Functioning, Disability and Health model. Therefore, more accurate assessments of community activity and participation should be investigated to better describe mobility function in lower-limb amputees.

2.6.3 Wearable technology to assess activity and participation

2.6.3.1 Accelerometers

Accelerometer based devices, often used to assess step count activity, work by assessing dynamic movements from deflection of a bar suspended by micro-

machined springs which provide resistance against acceleration (Culhane et al. 2005). Deflection of the bar is converted into acceleration readings. The use of accelerometers to assess body movement was first proposed in the 1950's (Gage 1964; Inman & Eberhart 1953). However given their size, unreliability and expense at that time, they were not widely used. Today, accelerometer based devices can be used to assess spatial-temporal gait parameters (e.g. stride time, step length, gait speed), sit to stand movements, posture changes, and activity (step counts) (Culhane et al. 2005).

2.6.3.2 Global positioning system

Global PS devices are another form of wearable technology potentially able to be used for monitoring activity and participation in the community. When combined with other forms of wearable technology, such as accelerometer based activity monitors, GPS devices can enhance data obtained by providing information regarding the context and location in which the activity is performed. Global PS devices work by receiving a signal from orbiting satellites to provide location (latitude and longitude) information. Direction and speed of GPS receivers can be calculated from changes in location. Position of a GPS receiver is determined from distance calculations between the GPS receiver and satellite using a minimum of three satellites and a mathematical technique known as trilateration (Maddison & Ni Mhurchu 2009) (see figure 2.2). Technology improvements have allowed for small and portable GPS devices to be commercially available at a reasonable cost. Additionally these devices are also capable of recording data over extended periods of time, substantially increasing their clinical application.

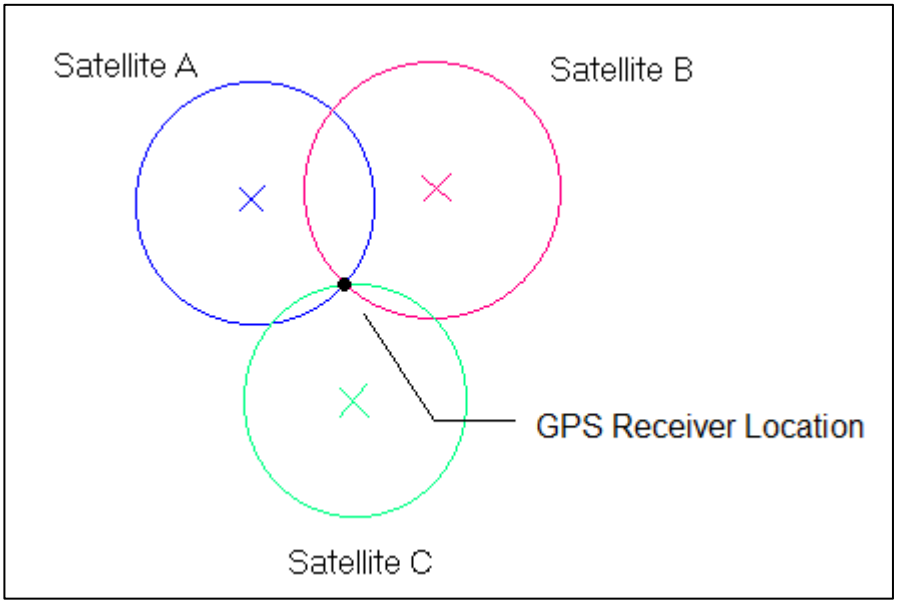

Figure 2.2: An example of how position of a GPS receiver is determined using a minimum of three satellites and a mathematical technique known as trilateration. Position of the GPS receiver is calculated by determining distance from the GPS receiver and each satellite.

2.6.3.3 How has GPS aided rehabilitation?

Approximately 17 years ago the potential of GPS as a promising tool to assess human mobility was identified (Schutz & Chambaz 1997). However, relatively few studies have investigated GPS in rehabilitation populations. A major limitation in the assessment of activity is the ability to identify the location where the activity has occurred. The addition of GPS to activity assessment studies may allow improved measurement of physical activity by providing positional information (Maddison & Ni Mhurchu 2009), speeds and distances travelled. In addition it may provide useful information assessing participation in the community by recording locations visited and where activity is performed (Chang, Coster & Helfrich 2013), and identify environmental barriers which may limit community activity and participation.

A recent review highlighted that GPS has been investigated as a tool to assess function for different population groups (Kerr, Duncan & Schipperjin 2011). Studies with healthy adults have investigated GPS and accelerometer devices to assess free-living activity (Rodríguez, Brown & Troped 2005; Saelens & Handy 2008; Terrier et al. 2000). Data from these studies were able to identify locations where activity occurred in the community. However, potentially more important to health research was the identification of locations where very little activity occurs. Given increases in chronic diseases associated with physical inactivity, ability to identify locations where physical activity is low may allow specific interventions to be investigated to increase physical activity levels. In addition, GPS has been used to simply measure time spent outdoors (Cooper et al. 2010) with potential implications for vitamin D deficient populations. Most commonly, GPS data identified participation in the community by recording location of recreational activities in children (Duncan, Badland & Schofield 2009; Maddison et al. 2010; Wiehe et al. 2008a; Wiehe et al. 2008b). With increasing childhood obesity (Weiss et al. 2004), activity assessments are important for health research in this population.

To date, studies using GPS to assess activity in rehabilitation patient populations is limited. In total, only seven studies were identified and all, bar one (Créange et al. 2007), were published within the last three years. These studies have either investigated patient activity for stroke patients (Evans et al. 2012; McCluskey et al. 2012), multiple sclerosis (Créange et al. 2007), transfemoral amputation (Jayaraman et al. 2014) or following orthopaedic surgery (Barzilay et al. 2011; Herrmann et al. 2011; Storey et al. 2013). The use of GPS was found to be a feasible and reliable

method of collecting community visit data (McCluskey et al. 2012). Accuracy of GPS data was also shown to be superior to that of self-reported travel diaries (McCluskey et al. 2012). Global PS devices were primarily used to identify community visits out of home (Evans et al. 2012; Herrmann et al. 2011; Jayaraman et al. 2014; McCluskey et al. 2012), or speeds and distances travelled (Barzilay et al. 2011; Créange et al. 2007). While some studies supplemented GPS devices with accelerometers to assess activity in greater depth (Evans et al. 2012; Herrmann et al. 2011; Jayaraman et al. 2014; Storey et al. 2013), data from these two devices were kept separate with only a single case study linking data to provide detailed information on activity in various community locations (Jayaraman et al. 2014). Clinical assessments of function were only moderately correlated to GPS data (Créange et al. 2007; Storey et al. 2013), suggesting that objective clinical assessments may not consider all aspects of community mobility. However it should be noted that the sample sizes of these identified studies were relatively small, with the largest study reporting on a sample of 31 participants (Créange et al. 2007), and three of the seven studies being either a case study (Evans et al. 2012; Jayaraman et al. 2014) or case series (Barzilay et al. 2011). Despite the relatively small sample sizes, useful information was provided by the GPS devices, confirming the ability of GPS to aid the assessment of mobility function (Kerr, Duncan & Schipperjin 2011).

2.6.3.4 Wearable technology to assess function in lower-limb amputees

Pedometer or accelerometer based devices have previously been used to assess function in lower-limb amputees. These studies have assessed activity to investigate effectiveness of prosthetic componentry (Berge, Czerniecki & Klute 2005; Coleman et al. 2004; Gailey et al. 2012; Klute et al. 2006), validate new assessments of

activity (Bussmann et al. 1998; Bussmann et al. 2004; Day 1981; Dudek et al. 2008; Holden, Fernie & Soto 1979; Ramstrand & Nilsson 2007), or more recently, assess accuracy of clinical subjective and objective measures of activity (Parker et al. 2010; Stepien et al. 2007). Further analysis of the data indicates amputees achieve a range of daily step counts from 2000 steps per day (Coleman et al. 2004; Holden & Fernie 1987) to 6000 steps per day (Stepien et al. 2007). As expected, transtibial amputees achieve a higher number of steps per day than transfemoral amputees (Klute et al. 2006). In addition greater step counts were observed on weekdays in comparison to weekends (Klute et al. 2006). Interestingly, the daily step counts reported for lower-limb amputees are similar to that of chronic stroke patients (6000 steps per day) (Haeuber et al. 2004), but substantially lower than that suggested for active healthy adults (10,000 steps per day) (Tudor-Locke & Bassett Jr 2004). This data provides insight into the low activity levels of amputees in general and highlights the mobility impairments faced by this population. The difference in step counts between lower-limb amputees and healthy adults is likely related to traits of amputee gait which often lead to impaired mobility and a decrease in community ambulation. Amputee gait is characterised by a reduction in gait speed (Genin et al. 2008), increased metabolic cost of walking and decreased mobility endurance (Gailey et al. 1994; Genin et al. 2008; Sansam et al. 2009; Schmalz, Blumentritt & Jarasch 2002; Waters et al. 1976).

Recently a single case-study was published where a GPS and accelerometer device were used to collect data from a single vascular transfemoral amputee (Jayaraman et al. 2014). This is the only identified study were both devices were provided to an amputee to assess functional mobility. Data obtained was able to provide greater

detail of functional mobility as both activity and movements in the community were assessed. This study demonstrated the potentially useful information both GPS and accelerometers can provide. Linking data and identifying locations in the community where mobility may be high or low has important implications for clinical rehabilitation practice.

As demonstrated by this case study, application of wearable technology may have wider and more significant value in lower-limb amputee clinical practice than simply assessing daily step counts. Firstly, as activity and participation is a key domain of the International Classification of Functioning, Disability and Health (WHO 2001, 2002), accurate assessment of these domains is important to understand disability. Achieving optimal activity and participation should be the primary aim of rehabilitation clinicians, and therefore, accurate measures are required to assess activity and participation in the community. Second, wearable technology has potential to assist clinical decisions. Inappropriate prescription of prosthetic componentry may affect an amputees comfort and mobility (Klute, Kallfelz & Czerniecki 2001), thereby limiting community activity and participation. Currently there is little information for outcomes that may be reliably used to aid selection of prosthetic componentry (Czerniecki 2005; Van Der Linde et al. 2004b). Accelerometer and GPS devices used together may be suitable to guide appropriate prosthetic prescription and confirm that optimal activity and participation levels are being achieved. In addition it may prove to be an accurate objective assessment of mobility function to assess outcomes from rehabilitation service, or new interventions aimed at improving activity and participation. Wearable technology is

likely to aid clinical practice in many ways and its potential should be further investigated.

In summary, advances in wearable technology may now allow reliable, objective data of community activity and participation to be obtained. Current methods of assessing activity and participation primarily involve clinical objective or subjective assessments, and it has been demonstrated that these measures may not accurately reflect activity and participation. As these outcomes are important domains of the International Classification of Functioning, Disability and Health (WHO 2001, 2002), accurate assessment is important for amputee rehabilitation. Given the relative lack of information around the application of accelerometer and GPS assessments in transtibial amputees, these instruments should be considered as a new methodology to assess mobility function in transtibial amputees.

2.7 Amputee Neurophysiology and Motor Control

This review has highlighted that movement of the lower-limb for mobility requires coordination of a number of components in the central nervous system including the motor cortex, sensory cortex, cerebellum, basal ganglia, visual cortex, vestibular and proprioceptive systems (Hausdorff 2007). It is well established that amputation of a limb leads to reorganisation of the motor cortex (Chen et al. 1998a; Fuhr et al. 1992), which may affect function. To understand the association between cortical neurophysiology and gait function, current evidence for neurophysiological reorganisation following amputation will first be reviewed. This will be followed by a review of the potential implication that reorganisation of the motor cortex may

have on gait function to determine if patterns of cortical reorganisation are adaptive (associated with good gait function) or maladaptive (associated with poor gait function).

2.7.1 Neuroplasticity

Neuroplasticity describes the ability of the central nervous system to modify its structural and functional connections in response to injury, behavioural changes or environmental challenges (Pascual-Leone et al. 2011). The process of brain neuroplasticity occurs constantly, but may be enhanced in certain environments such as after injury (e.g. amputation) or when learning new skills (e.g. rehabilitation). The term ‘adaptive neuroplasticity’ describes a process where reorganisation of the nervous system results in an improved functional outcome, while ‘maladaptive neuroplasticity’ describes a process where reorganisation of the nervous system results in a poor functional outcome. In rehabilitation, promoting adaptive neuroplasticity is important to optimise recovery of function after injury. Neuroplasticity may be seen as a continuum from short term changes in efficiency or strength of a few synaptic connections, to long term structural changes in the organisation and numbers of connections among neurons within a brain region or between different but functionally connected brain areas (Shumway-Cook 2012).

2.7.1.1 Neuroplasticity resulting from amputation of a limb

There is a substantial volume of human and animal literature indicating cortical reorganisation occurs following peripheral injury (e.g. amputation) (Brasil-Neto et al. 1992; Brasil-Neto et al. 1993; Cohen et al. 1991; Donoghue & Sanes 1988; Donoghue, Suner & Sanes 1990; Fuhr et al. 1992; Hall et al. 1990; Kaas, Merzenich

& Killackey 1983; Merzenich, Nelson & Stryker 1984; Recanzone et al. 1992; Sanes et al. 1988). In addition, subcortical structures such as the thalamus (Florence, Hackett & Strata 2000; Jones & Pons 1998; Nicolelis et al. 1993), brainstem (Florence & Kaas 1995; Lane et al. 1995) and spinal cord (Florence & Kaas 1995) are also known to reorganise following amputation.

Early animal studies were instrumental to the understanding of reorganisation in the cortical and subcortical brain following amputation. In addition to amputation, peripheral lesions such as motor nerve lesion (Donoghue, Suner & Sanes 1990), and deafferentation (Merzenich et al. 1983) have been studied as models of amputation in animals. The capacity of the cortex to reorganise following peripheral manipulation was first demonstrated clearly in the non-human primate in the early 1980s (Merzenich et al. 1983; Merzenich, Nelson & Stryker 1984). Since this early work, further basic neuroscience studies have demonstrated that the central nervous system possesses the ability to remodel itself. Following amputation of a digit in a range of animal species, the contralateral primary sensory cortex reorganises topographically to occupy the majority of the cortical territories formally representing the amputated digit (Kelahan & Doetsch 1984; Kelahan, Ray & Carson 1981; Merzenich, Nelson & Stryker 1984; Rasmusson 1982; Rasmusson & Turnbull 1983). Deprived areas within the contralateral sensory cortex were activated by stimulation or sensory input from adjoining digits or parts of the hand indicating an expansion of neighbouring representations. In a similar manner, reorganisation of the contralateral M1 was also observed. Amputation of a digit resulted in expansion of neighbouring representations formerly occupied by the amputated digit (Donoghue & Sanes 1988; Sanes, Suner & Donoghue 1990). The result was increased contralateral cortical

excitability of these expanded representations within hours of the injury (Donoghue & Sanes 1988; Donoghue, Suner & Sanes 1990; Sanes, Suner & Donoghue 1990).

Similar findings have been made in human studies. Using transcranial magnetic stimulation (TMS), stimulation of the former amputated limb (deafferentated limb) cortical representation evoked responses in muscles proximal to the site of amputation (deafferentation) (Brasil-Neto et al. 1993; Chen et al. 1998a; Cohen et al. 1991; Fuhr et al. 1992; Hall et al. 1990; Werhahn et al. 2002). Increased cortical excitability was observed following stimulation at these sites. Similarly cortical reorganisation was also demonstrated with functional magnetic resonance imaging (MRI) where enlargement of neighbouring representations was observed in both the sensory and motor cortex (Cruz et al. 2003b; Lotze et al. 2001; Simões et al. 2012) (see figure 2.3). Both TMS and functional MRI demonstrate cortical reorganisation in human amputees.

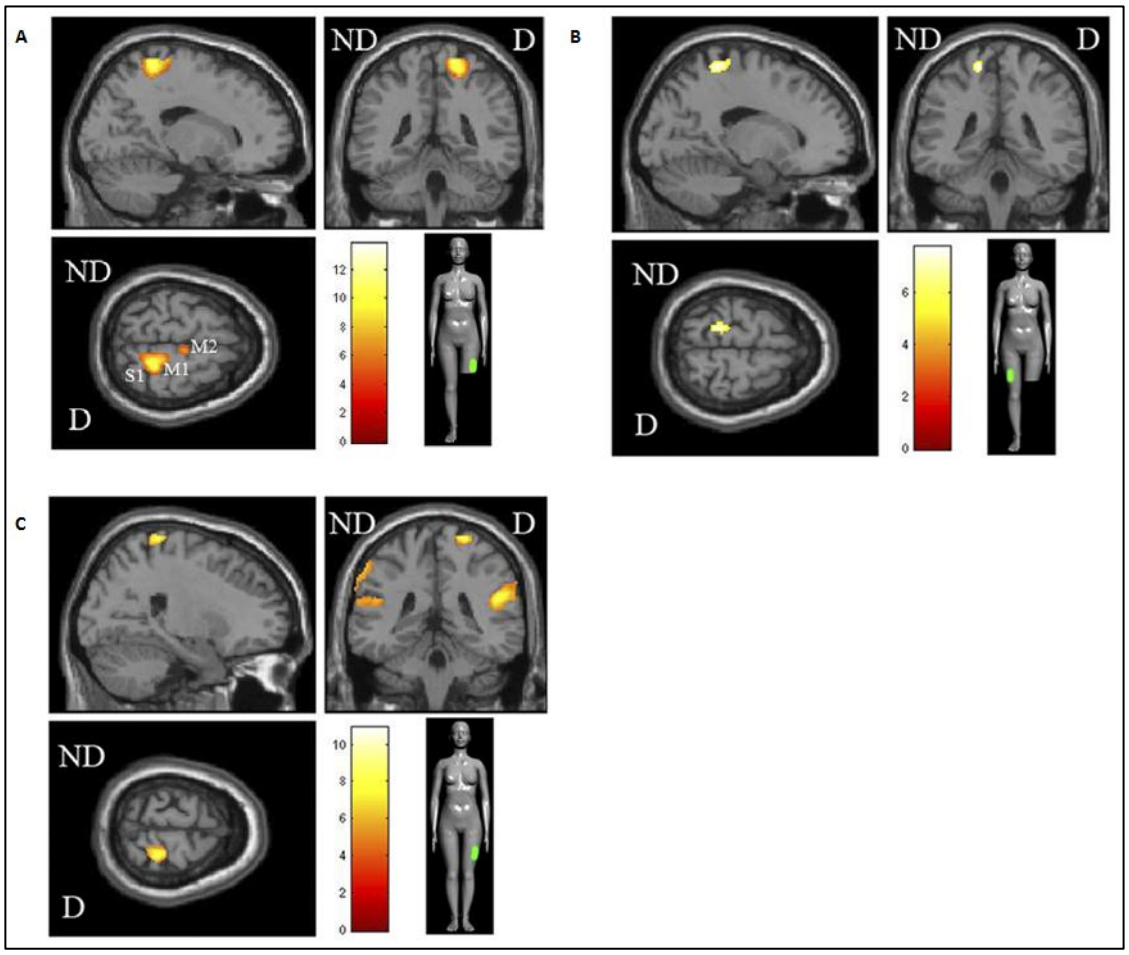

Figure 2.3: Functional MRI activation maps during tactile stimulation.

Location of tactile stimulation over the thigh is demonstrated in the figure of a human. A) Tactile stimulation of the amputated limb, proximal to site of amputation. B) Tactile stimulation of the homologous region on the non-amputated limb. C) Tactile stimulation of the region homologous to the amputee stump in control subjects. Figures demonstrate increased cortical representations in the primary sensory cortex proximal to site of amputation.

ND; non-amputated hemisphere, D; amputated hemisphere

Adapted from Simões et al. (2012)

Despite similarities between the findings of animal and human work into cortical reorganisation following amputation, there are potentially significant differences which must be taken into consideration. The site of reorganisation following limb amputation in humans is predominantly cortical (Chen et al. 1998a; Fuhr et al. 1992), which is different to animal models where substantial reorganisation occurs in both cortical and subcortical structures. For animal models, subcortical reorganisation at the spinal cord and brainstem has been reported. Following amputation of the hand in monkeys, afferent projections from the proximal forelimb sprouted into portions of the dorsal horn of the spinal cord and cuneate nucleus of the brainstem which were formerly recipients of afferents from the hand area (Florence & Kaas 1995). Reorganisation of the thalamus was also observed, specifically in the ventral posterior medial nucleus following deafferentation in rodents (Nicolelis et al. 1993) and the ventral posterior nucleus following amputation in monkeys (Florence, Hackett & Strata 2000). Cortical reorganisation is well documented in animals. Following hand amputation in monkeys, tactile stimulation to the forelimb and face were able to activate portions of the primary sensory cortex formerly driven by inputs from the hand (Florence & Kaas 1995; Kelahan, Ray & Carson 1981; Merzenich et al. 1983). These findings indicate reorganisation following amputation in animal models occurs at multiple levels.

In humans, reorganisation associated with amputation predominantly occurs at the level of the cortex, rather than in subcortical structures. Invasive techniques such as inserting microelectrodes into the cortex to assess neuronal activity in anaesthetised animals cannot be performed in humans. Alternatively non-invasive stimulation techniques provide useful neurophysiological information. Transcranial MS over M1

predominantly activates pyramidal tract neurons via superficial cortical interneurons and reflects neuronal excitability, while transcranial electrical stimulation activates pyramidal tract axons directly and is therefore less sensitive to M1 excitability (Day et al. 1989; Nakamura et al. 1996; Rothwell et al. 1991). For both lower-limb amputation and limb deafferentation it was demonstrated that cortical representations proximal to the level of amputation (deafferentation) were more excitable (demonstrated as larger motor evoked potentials) compared to homologous representations on the opposite limb for TMS, but not transcranial electrical stimulation (Brasil-Neto et al. 1993; Chen et al. 1998a). This finding indicates greater excitability of the neurons contributing to proximal muscle representations in M1 after amputation.

Current literature is less supportive of changes in spinal excitability following amputation in humans. Previous studies have demonstrated no difference between the amputated and non-amputated side for the percentage of the motoneuron pool activated by spinal electrical stimulation, which activates descending motor tracts in the spinal cord (Brasil-Neto et al. 1993; Chen et al. 1998a). However, the percentage of the motoneuron pool activated by TMS was shown to be larger on the amputated (deafferentated) side compared to the opposite limb (Brasil-Neto et al. 1993; Chen et al. 1998a; Cohen et al. 1991). Combining findings from spinal electrical stimulation and TMS indicates reorganisation predominantly occurs supraspinally. In addition, analysis of the H reflex to assess spinal motoneuron excitability found no difference between amputated and non-amputated sides (Brasil-Neto et al. 1993; Chen et al. 1998a; Fuhr et al. 1992). This further confirms that reorganisation following amputation occurs proximal to the spinal cord in humans.

Modulation of brainstem excitability following limb deafferentation has not been definitively demonstrated in humans. Similar to amputation, limb deafferentation was found to increase excitability of the contralateral M1 with TMS. However, motor responses to brainstem electrical stimulation remained unchanged (Werhahn et al. 2002). Although not tested in amputees, limb deafferentation models indicate the increased excitability of responses evoked by TMS is likely to be of cortical origin. Motor responses to brainstem electrical stimulation remained unchanged, therefore it is unlikely that reorganisation at the level of the brainstem has contributed to greater excitability of responses evoked by TMS.

There is some suggestion of reorganisation in the thalamus following amputation and limb deafferentation in humans. Stimulation of the region of the thalamus that originally represented the amputated limb was found to evoke sensations in the phantom limb (Davis et al. 1998). Furthermore, for the principal sensory nucleus of the thalamus, the region where the amputated (or deafferentated) limb would normally be represented was re-innervated by nearby intact representations (Davis et al. 1998; Kiss, Dostrovsky & Tasker 1994; Lenz et al. 1998). However, the degree to which reorganisation at the cortical level is driven by subcortical reorganisation is unclear. Animal models suggest reorganisation of the primary sensory cortex from amputation is predominately the result of changes in intrinsic cortical excitability and not secondary to subcortical reorganisation (Stojic, Lane & Rhoades 2001). However, this is yet to be confirmed in humans.

When considering this body of evidence, it appears reorganisation associated with limb amputation occurs predominantly in the sensorimotor cortex, with some further suggestion of thalamic reorganisation in humans. These results are dissimilar to those from animal models, which provide substantial evidence that reorganisation occurs both cortically and sub-cortically. The difference between animal and human reorganisation following amputation may relate to technical limitations of neurophysiological examinations in humans which are limited to non-invasive techniques such as TMS.

2.7.1.2 Modulation of cortical excitability following amputation

Various mechanisms may be associated with modulation of cortical excitability following amputation. Identification of these mechanisms has improved neurophysiological understanding of cortical reorganisation related to amputation. It is well established that amputation results in increased cortical excitability, demonstrated as larger motor evoked potentials (MEPs) evoked by TMS (Cohen et al. 1991; Gagné et al. 2011; Irlbacher et al. 2002; Ridding & Rothwell 1997; Röricht et al. 1999). Larger MEPs suggests modulation of synaptic transmission via glutamate receptors, representing long-term potentiation like synaptic plasticity (Delvendahl et al. 2012). However, output from M1 is the net result of multiple systems that exert excitatory and inhibitory influences on corticospinal neurons (Chen et al. 2008), and these may also be investigated using TMS or pharmacology.

Following amputation, animal studies suggest that modulation of the cortex is likely mediated by gamma-aminobutyric acid (GABA) inhibition (Jacobs & Donoghue 1991; Jones 1990a). Similarly for humans, both upper- and lower-limb amputee

studies demonstrate a reduction of GABAergic inhibition in M1 (Chen et al. 1998a; Schwenkreis et al. 2000). Gamma-aminobutyric acid is an important inhibitory neurotransmitter in the cortex and constitutes approximately 25-30% of the neuronal population (Jones 1993). Gamma-aminobutyric acid neurons are considered to be crucial to the maintenance of cortical motor representation (Jacobs & Donoghue 1991), and the modulation of GABA receptor activity is thought to indicate reorganisation. Interestingly, reduced excitability of GABA neurons in amputees was observed many years after the amputation (Chen et al. 1998a; Schwenkreis et al. 2000), potentially indicating ongoing modulation within M1. Modulation of N-methyl-D-aspartate (NMDA) receptors was also demonstrated in transhumeral upper-limb amputees (but not transradial amputees) (Schwenkreis et al. 2000). However, this mechanism for reorganisation is yet to be established in lower-limb amputees.

2.7.2 The Ipsilateral Cortex

The majority of work investigating reorganisation after lower-limb amputation has focussed on the contralateral cortex. However, it has also been demonstrated that the ipsilateral cortex may reorganise following amputation. A few studies using imaging techniques of functional MRI or positron emission tomography have indicated that movement of the amputated limb activates the primary motor and sensory cortex of both hemispheres (Cruz et al. 2003b; Dettmers et al. 1999; Kew et al. 1994; Simões et al. 2012). Although understanding the implications and mechanisms of ipsilateral primary motor and sensory cortex activation was not the primary purpose of those studies, it was identified that the abnormally increased ipsilateral cortical blood flow was present in traumatic amputees and not congenital amputees (Kew et al. 1994),

potentially indicating a mechanism for ipsilateral M1 reorganisation. Reorganisation of the ipsilateral M1 was also reported with TMS mapping studies which found a lateral shift of the ipsilateral motor map compared to control subjects (Schwenkreis et al. 2003). However, given technical limitations of lower-limb TMS mapping due to the location of M1 lower-limb representations, and spatial resolution of TMS, these results should be interpreted cautiously.

Mechanisms mediating ipsilateral M1 reorganisation may be similar to that of the contralateral M1. Bilateral upregulation of $GABA_A$ receptors was found in upper-limb amputees in a positron emission tomography study and is likely to be a mechanism contributing to bilateral reorganisation of the motor and sensory cortex (Capaday et al. 2000). Further, previous studies have suggested reorganisation of the ipsilateral motor and sensory cortex may result from modulation via interhemispheric inhibition (Capaday et al. 2000; Kew et al. 1994; Werhahn et al. 2002). Interhemispheric inhibition was first observed with a dual coil, paired-pulse, TMS paradigm. Stimulation of M1 over one hemisphere delivered 6-30ms prior to stimulation over the opposite hemisphere was found to inhibit the MEP evoked from that M1 (Ferbert et al. 1992). Inhibition of the MEP is believed to be produced via a transcallosal pathway connecting M1 hand representations between hemispheres (Ferbert et al. 1992; Meyer et al. 1995). Interhemispheric inhibition may be driven by reduction in intracortical inhibition in the contralateral M1 observed following amputation (Chen et al. 1998a; Schwenkreis et al. 2000). An alternative explanation for ipsilateral M1 reorganisation may be that increased use of the sound limb would increase the cortical response (Schwenkreis et al. 2003; Simões et al. 2012). The increased cortical excitability may drive the reorganisation observed in the ipsilateral

motor and sensory cortex. Greater understanding of these mechanisms leading to ipsilateral M1 reorganisation may be important to investigate to further understand human amputee neurophysiology.

Similar to amputation, bilateral cortical reorganisation has also been reported after stroke. Following a stroke, stimulation with TMS of the ipsilesional hemisphere has shown there are higher stimulation thresholds, lower corticomotor excitability and longer MEP latencies when compared to the contralesional hemisphere (Catano et al. 1996; Koski, Mernar & Dobkin 2004; Rossini & Pauri 2000; Talelli, Greenwood & Rothwell 2006; Traversa et al. 2000; Traversa et al. 1998). Along with suppression of ipsilesional hemisphere excitability, there is also facilitation of the contralesional hemisphere, resulting in interhemispheric 'imbalance' (see figure 2.4) (Grefkes & Fink 2011; Grefkes et al. 2008; Murase et al. 2004; Shimizu et al. 2002; Ward et al. 2006). Imbalance of the interhemispheric inhibitory pathway increases the inhibitory influence from the contralesional M1 to the ipsilesional M1 and reduces the inhibitory influence from ipsilesional M1 to contralesional M1. Interhemispheric projections are thought to activate inhibitory intracortical interneurons in the target M1, suppressing corticospinal output (Di Lazzaro et al. 1999; Ferbert et al. 1992). Therefore, this imbalance would further suppress cortical excitability of the ipsilesional M1 and facilitate the contralesional M1 resulting in bilateral cortical reorganisation. This model of bilateral cortical reorganisation may be different to that of amputation, but may assist understanding of the neurophysiology of bilateral reorganisation observed in amputees.

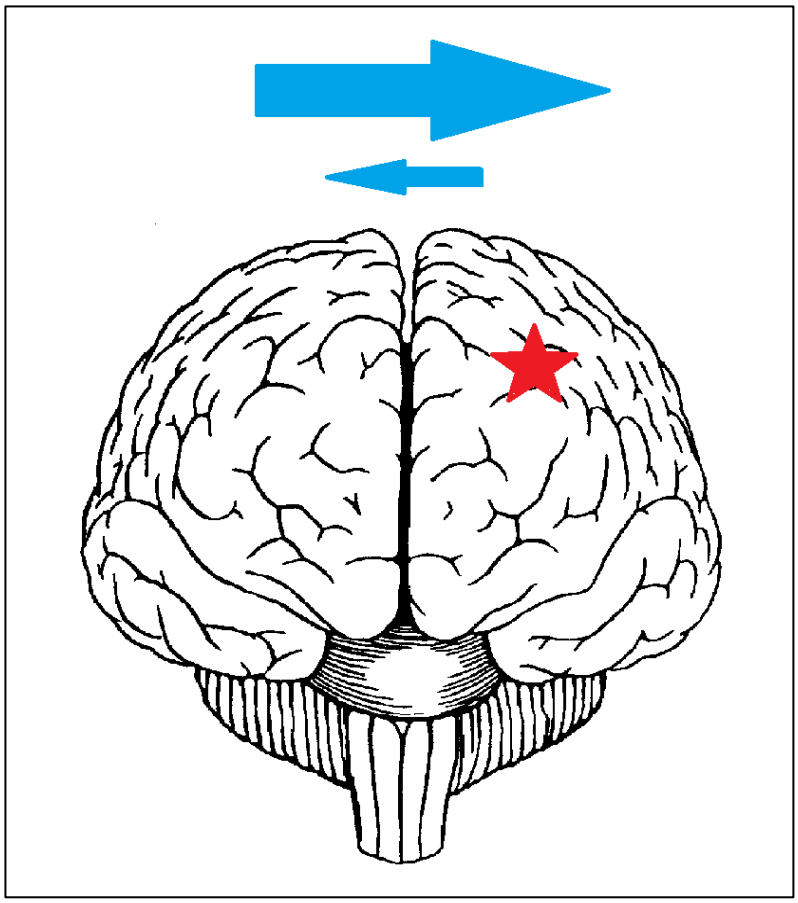

Figure 2.4: A representative diagram demonstrating the imbalance of interhemispheric inhibition following stroke.

Hemisphere with stroke lesion is indicated with a star. Relative strength of interhemispheric inhibition is demonstrated with size of the arrows.

Excitability of interhemispheric projections between hemispheres has not been assessed in amputees. There is suggestion that limb deafferentation can modulate interhemispheric inhibition, potentially contributing to bilateral reorganisation within M1 (Werhahn et al. 2002). However, these changes were only observed distal to the level of deafferentation, meaning this finding may not be applicable to amputees where representations proximal to the level of amputation are of interest. Further

studies are required to confirm interhemispheric projections contribute to bilateral M1 reorganisation in amputees.

2.7.2.1 Functional implication of the ipsilateral M1

It is possible that increased excitability of the ipsilateral M1 may impact on function and control of the lower-limb. Function may be influenced through ipsilateral projections to spinal motoneurons innervating that limb, modulation of interhemispheric projections to the contralateral M1, or both (Bradnam, Stinear & Byblow 2013; Perez & Cohen 2008; Ziemann et al. 1999). Functional implications of ipsilateral M1 reorganisation have not been investigated in lower-limb amputees. This information may be important to understand amputee motor control.

2.7.3 Motor control

Safe, precise and efficient movement is an essential trait of human function, and the central nervous system plays an important role in execution of this task. Motor control is the ability to regulate and direct these essential mechanisms to execute the desired movement (Shumway-Cook 2012). Good motor control is essential for human locomotion, and there appears to be a gap in the literature around amputee motor control and gait function both over prosthetic rehabilitation and following completion of rehabilitation. Therefore it is necessary that neurophysiology of motor control is further investigated in lower-limb amputees.

2.7.3.1 Motor control of locomotion in animals

Much of the early understanding of motor control for locomotion was obtained from animal studies. As early as 1911 it was demonstrated that in cats with an induced

spinal lesion, an alternating pattern of activity in antagonistic muscles could be produced to achieve locomotion (Brown 1911). Therefore it was proposed that the spinal cord must contribute significantly to the locomotion pattern, perhaps with minimal supraspinal influence. Later studies have confirmed that the spinal network has the capacity to generate complex, but stereotypical, patterns of motor output which are similar to locomotion in the absence of supraspinal or sensory input in animals (Grillner 1985; Jordan 1998). Commands are generated sequentially in time during each step by neural networks located in the spinal cord called central pattern generators (Grillner et al. 1991; Lacquaniti, Ivanenko & Zago 2012). However, transection of the spinal cord in cats does not produce perfected locomotion patterns. Obvious deficits include absence of voluntary and equilibrium controls, as well as changes in the synchronisation of flexor muscles acting at various joints. This results in varying degrees of foot drag at onset of swing phase and some failures in stepping (Rossignol 2000). In addition, stimulation of the midbrain evokes locomotion in spinalised cats, with increasing intensity facilitating the walking gait into running. This relationship between stimulation intensity of the midbrain and gait patterns (walking and running) may indicate changes in excitability of the midbrain regulate control of walking and running (Shik, Severin & Orlovskii 1966).

While cat studies demonstrate importance of spinal contribution to walking, studies in non-human primates demonstrate that spinal networks depend more on supraspinal control to work properly than is the case in other animal models (Eidelberg, Walden & Nguyen 1981; Fedirchuk et al. 1998). Spinalised monkeys were unable to produce stepping patterns similar to that produced in the cat. However, stepping patterns were generated by electrical stimulation delivered proximally at the posterior subthalamic

region and midbrain tegmentum (Eidelberg, Walden & Nguyen 1981). Drug administration also evoked stepping patterns, although only the adrenergic agonist, Clonidine, consistently produced a stepping pattern for all monkeys (Fedirchuk et al. 1998). These results indicate that non-human primates also possess a spinal network capable of eliciting rhythmic alternating activity for stepping.

2.7.3.2 Motor control of locomotion in humans

The importance of a cortical contribution to the normal gait pattern appears to be substantially different between humans and animals. Several levels of the motor system are involved in the generation of gait in humans, likely due to more complex bipedal gait patterns (Jahn et al. 2008). Descending pathways from higher centres and sensory feedback from the periphery allow variation and adaptability in locomotor patterns to meet environment and task demands (Jordan 1998; Nielsen 2003). Human motor control has greater dependency on supraspinal control with significant contribution to the control of muscle activity by direct monosynaptic corticospinal pathways from M1 to spinal motoneurons (Christensen et al. 1999; Nielsen 2003). The cortex, brainstem and cerebellum provide descending input to modify and adapt the gait patterns for the required task (Duysens & Van de Crommert 1998). Evidence of the importance of the cortex is clearly demonstrated from M1 lesions which have greater detrimental effects on gait function in humans compared to animals (Porter & Lemon 1993). In support, increased blood flow in lower-limb sensorimotor cortical areas was demonstrated during treadmill walking in humans (Fukuyama et al. 1997), indicating increased cortical activity during gait. The human M1 is likely associated with the timing of muscle activity in gait (Capaday et al. 1999), with transmission in the corticospinal tract shown to be greatly

increased during the walking cycle (Capaday et al. 1999; Petersen, Christensen & Nielsen 1998), further highlighting importance of M1 during gait.

The brainstem and cerebellum also have important contributions to the network of supraspinal locomotor control. A functional MRI study found that motor imagery of standing, walking and running activated regions of the cerebellum and brainstem which are involved in speed regulation and pace making during locomotion (Jahn et al. 2008). One review highlighted that the contemporary understanding of the cerebellum contribution to gait is determined by three regions of the cerebellum; the medial, intermediate and lateral (Morton & Bastian 2007). The medial region regulates dynamic balance and rhythmic flexor/extensor activity. The intermediate cerebella region controls timing, amplitude and trajectory of movement and the lateral region is responsible for adjusting the locomotor pattern during complex situations. The functional specificity of these regions was further confirmed from a study involving patients with various cerebellar lesions and gait irregularities (Ilg et al. 2008). These findings confirm contributions of the brainstem and cerebellum in the production and control of gait.

2.7.3.3 Bilateral cortical innervation of proximal lower-limb muscles

The capacity of supraspinal structures to provide descending input to spinal motoneurons is significant for the production of movement. Hemispheric lateralisation describes the dominance of either the left or right hemisphere in providing descending control over the contralateral limbs. In humans, it is widely accepted that the contralateral hemisphere provides sensorimotor control for the limbs. However, 10-15% of descending projections from M1 project to spinal

motoneurons of the ipsilateral proximal upper-limb in monkeys (Brinkman & Kuypers 1973; Kuypers 1964) and humans (Stephen et al. 2003). There are fundamental differences in the neural control of the upper- and lower-limbs, likely due to functional differences. In the lower-limb, bilateral activation of M1 was demonstrated during gait activity (Miyai et al. 2001). This bilateral activity may be a function of the behavioural context of the movement as gait requires activation of both lower-limbs. However, bilateral M1 activation of similar magnitude was also found during isolated knee flexion and extension movements (Luft et al. 2002). Similarly isolated foot dorsiflexion and plantar flexion activated M1 bilaterally (Miyai et al. 2001). For these studies bilateral M1 activation was related to unilateral movement of the lower-limb. Electromyography recording of the resting (non-active) lower-limb confirmed that it was at rest, indicating bilateral M1 activation was unlikely to be associated with movement of both lower-limbs. Together these findings suggest ipsilateral descending projections may provide descending control to spinal motoneurons of the lower-limb for normal motor control.

A potential explanation for bilateral M1 activation is that task complexity demands greater cortical contribution, as studies in the upper-limb suggest that bilateral cortical contribution to movement is associated with increased task complexity (Chen, Cohen & Hallett 1997; Chen et al. 1997; LaPointe et al. 2009; Lee et al. 2010; Perez & Cohen 2008; Verstynen et al. 2005). However, the isolated lower-limb movements identified previously would be considered simple tasks, and it may be less likely that bilateral control of the lower-limb is associated with task complexity. The most obvious explanation is that lower-limb motor control requires bilateral

cortical contribution to perform the basics of the task, as opposed to upper-limb movements which are more lateralised (Luft et al. 2002).

2.7.4 Ipsilateral M1 and motor control

Ipsilateral descending projections may have important functional implications after neurological damage and for rehabilitation. Reorganisation of M1 bilaterally has been associated with both amputation and stroke. Upregulation of the ipsilateral M1 for amputees, and contralesional M1 in stroke, may be associated with facilitation of ipsilateral descending projections to the spinal cord (Alagona et al. 2001; Caramia et al. 2000; Lewis & Perreault 2007; Netz, Lammers & Hömberg 1997; Turton et al. 1996). For stroke, where residual integrity of the corticospinal tract from the ipsilesional M1 is maintained, upregulated ipsilateral descending projections from the contralesional M1 seem to be associated with poor functional outcomes for both the lower-limb (Jayaram et al. 2012; Madhavan, Rogers & Stinear 2010) and upper-limb (Bradnam et al. 2012; Netz, Lammers & Hömberg 1997; Turton et al. 1996). Functional implications of ipsilateral descending projections is further supported by evidence indicating that contralesional M1 excitability decreases over time in well recovered stroke patients (Stinear et al. 2008). This finding indirectly suggests attenuation of ipsilateral projections to the paretic limb may be associated with improved function. In addition, non-invasive brain stimulation to suppress contralesional corticomotor excitability and ipsilateral projections in the upper-limb was able to improve function following stroke in individuals where integrity of the corticospinal tract was maintained (Boggio et al. 2007; Bradnam et al. 2012; Grefkes et al. 2010; Hummel et al. 2005; Kim et al. 2010; Nowak et al. 2010). These findings may indicate upregulated ipsilateral projections are functionally maladaptive.

2.7.5 Neurophysiological biomarkers of function

Understanding cortical reorganisation and neurophysiology of motor control of lower-limb amputees may assist identification of neurophysiological biomarkers of gait function. These biomarkers may be associated with adaptive (good function) or maladaptive (poor function) patterns of cortical reorganisation. Similar techniques have been previous used in people who have experienced stroke (Stinear et al. 2012). Assessment of upper-limb function, neurophysiology (TMS) and imaging (diffusion-weighted MRI) were combined in an algorithm to predict upper-limb function 12 weeks post stroke. The ability to predict functional recovery may assist streamlining of rehabilitation services and accurate rehabilitation goal setting for individual patients (Stinear et al. 2012).

For the stroke affected lower-limb, similar studies have identified measures of corticomotor excitability that are associated with lower-limb function (Jayaram et al. 2012; Madhavan, Rogers & Stinear 2010). It should be acknowledged that these studies did not test the predictive nature of these neurophysiological measures for functional recovery. Rather, they tested the association between function and neurophysiological measures. However, the results indicate a strong relationship between neurophysiological measures and function, suggesting these neurophysiological measures may be potential biomarkers for future studies. Future studies are required to test causation to confirm measures of corticomotor excitability are functional biomarkers.

Although few studies have investigated neurophysiological measures in lower-limb amputees, none have tested the association between such measures and functional ability. Research is required to address this gap in the literature and provide a greater understanding of human neurophysiology and function. Neurophysiological biomarkers should be identified that can be used clinically to predict functional recovery. Future studies may also investigate techniques to modulate neurophysiological measures and drive plasticity towards an adaptive pattern of cortical reorganisation in particular amputees identified by the same neurophysiological measures.

2.7.6 Transcranial magnetic stimulation as a tool to identify neurophysiological biomarkers of function

As identified above, TMS is a non-invasive method to obtain neurophysiological measures in the conscious human brain, which provide biomarkers of function and recovery. Transcranial MS is a non-invasive, painless, neurophysiological technique to stimulate the human brain through the intact skull (Barker, Jalinous & Freeston 1985). Shortly following delivery of the stimulus over M1 at sufficient intensity, TMS activates corticospinal output neurons resulting in a small twitch at the target muscle. This muscle twitch is measured using surface electromyography, and is known as a MEP (Di Lazzaro et al. 2004; Rothwell 1997). Assessing properties of the MEP with various stimulation techniques to probe cortical connections has advanced understanding of human neurophysiology and motor control in healthy adults and various pathological patient groups (Chen, Cohen & Hallett 2002; Chen et al. 2008; Edwards & Fregni 2008; Edwards, Talelli & Rothwell 2008; Hallett 2007; Rothwell 2011). Transcranial MS is an important neurophysiological tool, and when

associated with functional measures, may assist identification of functional biomarkers.

Magnetic stimulation with TMS is based on fundamental principles of electromagnetic induction which are known as Faraday's law. Briefly, the TMS stimulator generates a rapid high voltage current which is passed through a wire coil to produce a pulsed magnetic field of up to three Tesla (Barker, Jalinous & Freeston 1985). This fluctuating magnetic field evokes an electric current, known as an 'eddy' current, which flows in a nearby conductor, such as human tissue (Rothwell et al. 1991). It is likely that TMS stimulates axons of various neurons in the superficial grey matter, rather than cell bodies or initial segment regions (Barker, Garnham & Freeston 1991; Day et al. 1989; Maccabee et al. 1998; Rothwell 1997; Rothwell 2011). These axons may include intracortical excitatory and inhibitory interneurons, thalamo-cortical or cortico-cortical axons (Rothwell 1997; Rothwell et al. 1991). Corticomotor neurons within M1 are activated by indirect (trans-synaptic) stimulation (Di Lazzaro et al. 2004). With sufficient TMS intensity, an action potential is generated which leads to activation of spinal motoneurons and motor units in the target muscle and may result in a visible muscle twitch (Di Lazzaro et al. 2004; Di Lazzaro et al. 2008).

There are a number of neurophysiological measures which may be obtained using TMS. These measures may provide useful information to understand amputee neurophysiology, and may also have potential as biomarkers of functional recovery. Transcranial MS is commonly delivered as either single- or paired-pulse. For single-pulse TMS, assessment of motor thresholds and the amplitude of the MEP are two

common neurophysiological measures. Motor thresholds are determined at the cortical 'hotspot' for the targeted muscle, and are defined as the lowest stimulus intensity capable of eliciting a defined MEP (Rossini et al. 1999). Motor thresholds represent intrinsic excitability of intracortical axons and excitability of spinal motoneurons (Delvendahl et al. 2012). When a target muscle is in an active state (i.e. during a muscle contraction), excitability is increased and therefore active motor thresholds are lower than rest thresholds. Characteristics of the MEP, such as size and latency, provide information regarding excitability and impulse conduction characteristics of neurons in M1, the corticospinal tract and spinal motor centres (Chen et al. 2008; Hallett 2007; Rothwell 2012). Therefore, a combination of cortical and spinal excitability contributes to the size of the MEP (Rothwell et al. 1991). Stimulus-response curves are a relatively robust technique to assess corticospinal excitability across the range of excitable neurons. Stimulus-response curves are constructed by plotting average MEP amplitude against increasing TMS stimulation intensity. In healthy adults, stimulus response curves are sigmoidal in shape (Devanne, Lavoie & Capaday 1997), and the steepness of the stimulus response curves are likely related to strength of corticospinal projections to the spinal cord (Chen et al. 2008).

Intracortical circuits within the cortex may be assessed with paired-pulse TMS (Cheeran et al. 2010; Chen et al. 2008; Di Lazzaro et al. 2004), and a previous stroke study demonstrates potential for these measures to be biomarkers of function (Swayne et al. 2008). Activation thresholds between inhibitory and excitatory interneurons and the corticomotor neurons themselves differ, thereby allowing some selectivity of stimulation by the TMS coil (Di Lazzaro et al. 2004; Ilić et al. 2002). A

single-pulse MEP may be conditioned by a preceding pulse, either facilitating or suppressing the 'test' MEP depending on timing, intensity and type of conditioning stimulus. Paired-pulse TMS was first described in 1993 (Kujirai et al. 1993), and has been used extensively to investigate intracortical inhibitory and facilitatory circuits within M1. Intracortical circuits are probed by delivering two pulses separated by a short interval over M1 of one hemisphere. One of the most established measures is short-latency intracortical inhibition (SICI) (Kujirai et al. 1993). When testing SICI, the first pulse (conditioning stimulus) is subthreshold, and is not of sufficient intensity to generate an action potential and evoke a MEP on its own. However, it does activate the lower-threshold intracortical inhibitory neurons, which evoke an inhibitory post-synaptic potential in the target corticomotor neuron (Chen et al. 1998b; Di Lazzaro et al. 1998; Hanajima et al. 1998). The inhibitory post-synaptic potential leads to suppression of the MEP evoked by the second, suprathreshold stimulus (test stimulus), delivered 1-5ms after the conditioning stimulus (Kujirai et al. 1993). The degree of inhibition is normally quantified by comparing the conditioned MEP amplitude to the non-conditioned MEP amplitude and reported as a percentage. Pharmacology studies indicate SICI is likely mediated by $GABA_A$ receptor inhibition, as administration of $GABA_A$ receptor agonists lorazepam (Di Lazzaro et al. 2000; Di Lazzaro et al. 2005a; Di Lazzaro et al. 2005b; Ziemann et al. 1996a) and diazepam (Di Lazzaro et al. 2005b; Ilić et al. 2002) increase SICI.

Intracortical facilitation (ICF) is another paired-pulse intracortical excitability measure evoked by a similar TMS protocol to SICI, but at longer inter-stimulus intervals between conditioning and test pulses (6-20ms) (Kujirai et al. 1993; Ziemann, Rothwell & Ridding 1996). Pharmacology of ICF is not as well

characterised as SICI. However, it is suggested that ICF is most likely a net facilitation arising from relatively stronger facilitation and weaker inhibition of the non-conditioned MEP (Hanajima et al. 1998; Schwenkreis et al. 1999; Ziemann et al. 1998). A third paired-pulse TMS protocol to assess intracortical excitability is long-latency intracortical inhibition (LICI). Long-latency ICI employs two suprathreshold pulses at longer inter-stimulus intervals of 50-200ms (Di Lazzaro et al. 2002; Nakamura et al. 1997; Valls-Solé et al. 1992). Long-latency ICI is pharmacologically distinct from SICI, and is thought to be mediated by slow inhibitory post-synaptic potentials mediated by the $GABA_B$ receptor (McDonnell, Orekhov & Ziemann 2006; Sanger, Garg & Chen 2001; Werhahn et al. 1999).

Transcranial MS is generally considered a safe technique provided standard procedures and guidelines are followed (Rossi et al. 2009). Although rare, a potential adverse event for TMS is induction of a seizure, either during TMS or shortly after (Anand & Hotson 2002; Kratz et al. 2011; Pascual-Leone et al. 1992). Other potential adverse events include changes in mood or cognition, headaches, fatigue and tissue damage from skin preparation for surface electrodes (Rossi et al. 2009; Wassermann 1998). However, these events are uncommon, and evidence indicates that TMS is a safe technique provided guidelines and safety procedures are adhered to (Rossi et al. 2009). Because of this, TMS is an appropriate technique to probe cortical and intracortical excitability of amputees. Similar to stroke (Jayaram et al. 2012; Madhavan, Rogers & Stinear 2010; Stinear et al. 2012; Swayne et al. 2008), determining relationships between neurophysiological single- and paired-pulse TMS measures and function may provide TMS biomarkers of function. Such measures could assist clinicians by identifying patients at risk of poor recovery, streamlining

rehabilitation programs, determining appropriate rehabilitation goals, or identifying therapeutic interventions aiming to increase function. Neurophysiological TMS measures should be investigated to determine their use as functional biomarkers of recovery in lower-limb amputees and provide greater understanding of gait function.

2.7.7 Summary of amputee neurophysiology and motor control

Reorganisation of M1 occurs following amputation. Corticomotor and intracortical excitability of M1 bilaterally may be associated with amputee gait function, however previous studies have not investigated this potential relationship. It is possible that TMS measures of corticomotor and intracortical excitability of M1 bilaterally may identify good and poor functional recovery. Cortical correlates of gait function have significant potential to improve understanding of amputee neurophysiology and would likely improve clinical practice. These measures may identify patients at risk of maladaptive cortical neuroplasticity negatively impacting on recovery, or guide treatment decisions based on these functional biomarkers. Therefore TMS measures of corticomotor and intracortical excitability should be investigated as potential functional biomarkers.

2.8 Literature Review Summary

The increasing age and comorbidities of amputees is likely to challenge successful rehabilitation for vascular and diabetic amputees, so further understanding of gait and mobility function is required. Gait and mobility function are key rehabilitation outcomes for lower-limb amputees, yet relatively few studies have investigated alternative assessments gait and mobility function to improve understanding and knowledge of these important outcomes. New assessments of gait and mobility

function in lower-limb amputees have the potential to increase understanding of recovery, identify responders and develop new therapy interventions. These novel approaches must first be investigated to establish evidence supporting their use as appropriate assessments of gait and mobility function. In this thesis, the context clinicians currently work in is explored, and then three potential gait and mobility assessments are investigated.

The specific research questions which are addressed in the experiments of this thesis are;

- What outcomes are currently achieved by amputee rehabilitation units in Australia?
- Is the variability of speed normalised spatial-temporal gait parameters an important gait biomarker associated with falls history in transtibial amputees?
- Can wearable technology be used to assess community mobility function in transtibial amputees, and are measures of community mobility function associated with clinical assessments of normalised gait variability and falls history?
- Can TMS measures be used as neurophysiological biomarkers of gait function?

CHAPTER THREE: LOWER-LIMB AMPUTEE REHABILITATION IN AUSTRALIA: ANALYSIS OF A NATIONAL DATA SET 2004 - 2010

About this chapter:

The purpose of this chapter was to review the national amputee rehabilitation outcomes dataset to identify complexities and challenges facing amputee rehabilitation in Australia. There is a particular focus on demographics and clinical characteristics of amputees admitted for prosthetic rehabilitation and how these characteristics have changed over the years of observation. This chapter specifically addressed the research question 'What outcomes are currently achieved by amputee rehabilitation units in Australia?', and provides information of the context that clinicians work in. This is the first analysis of the national dataset focussed on amputees and the results were published in *Australian Health Review*.

3.1 Abstract

The purpose of this study was to examine demographics, clinical characteristics and rehabilitation outcomes of lower-limb amputees, using the Australasian Rehabilitation Outcomes Centre (AROC) database. Lower-limb amputee rehabilitation separations between 2004 and 2010 were identified using AROC impairment codes 5.3–5.7 (Australasian Rehabilitation Outcome Centre 2007). Analysis was conducted by year, impairment code, Australian National Sub-acute and Non-Acute Patient (AN-SNAP) classification (S2–224, functional independence measure (FIM) motor score 72–91; S2–225, FIM motor score 14–71) and states of Australia. Mean length of stay (LOS) for all lower-limb amputee episodes was 36.1 days (95%CI: 35.4–36.9). Majority of episodes were unilateral below knee (63.6%), males (71.8%) with a mean age of 67.9 years (95% CI: 67.6–68.3). Year-on-year analysis revealed a trend for increasing LOS and decreasing age. Analysis by impairment code demonstrated no significant difference in rehabilitation outcomes. Analysis by AN-SNAP found that LOS was 16.2 days longer for S2–225 than for S2–224 (95% CI: 14.7–17.8, $p < 0.001$), and FIM (mot) change was 12.0 points higher for S2–225 than for S2–224 (95% CI: 11.5–12.6, $p < 0.001$). Analysis by states revealed significant variation in LOS, FIM (Mot) change and FIM (Mot) efficiency which may be associated with variations in organisation of rehabilitation services across states. Although amputees represented a comparatively small proportion of all rehabilitation episodes in Australia, their LOS was significant. Unlike many other rehabilitation conditions, there was no evidence of decreasing LOS over time. AN-SNAP classes were effective in distinguishing rehabilitation

outcomes, and could potentially be used more effectively in planning rehabilitation programs.

3.2 Introduction

Worldwide incidence of lower-limb amputation is highly variable with incidence rates ranging from 5.8 to 31 per 100 000 (Moxey et al. 2011). Most lower-limb amputees in the developed world are elderly vascular patients often presenting with diabetes mellitus (Nehler et al. 2003; Pernot et al. 2000; Stone et al. 2007). It is estimated that 700 000 Australians (3.6% population) were diagnosed with diabetes mellitus, and 3394 diabetic related lower-limb amputations were performed in Australia in 2004–05 (Australian Institute of Health and Welfare 2008).

Amputees are a core group in Australian rehabilitation units who have a long index LOS. The long LOS associated with the index admission is justified by clinicians as important because restoring independent mobility and community integration reduces the larger social and health service costs associated with disability (Pell et al. 1993). It is widely believed that growth of interventional vascular surgery has helped reduce or postpone lower-limb amputation numbers in vascular patients (Feinglass et al. 1999; Nowygrod et al. 2006). However, it is unknown whether amputees entering rehabilitation units now present with different demographics than previously. This may result in a change in the outcomes achieved, time taken to achieve these outcomes or in the nature of the clinical programs provided. National outcome data collected by AROC will allow further investigation into the demographics, clinical characteristics and rehabilitation outcomes across Australia.

Australasian ROC collects standardised data for each and every episode of inpatient rehabilitation care from rehabilitation services in Australia (private and public). It provides a national benchmarking service, as well as information to improve understanding of factors that influence rehabilitation outcomes and costs. The objective of this study was to examine the AROC database for inpatient lower-limb amputee rehabilitation episodes to understand the demographics, clinical characteristics and rehabilitation outcomes. Service implications for lower-limb amputees in Australia will be drawn from these findings. The primary outcomes of interest will include improvement in patient functional status, hospital LOS, clinical characteristics and discharge destination. In addition, the yearly trends in episode outcomes and service efficiency will be examined, as well as comparison of outcomes for service provision between impairment codes, AN-SNAP classifications, and states of Australia.

3.3 Methods

3.3.1 Design

This study was a retrospective analysis of lower-limb amputee rehabilitation outcomes for separation episodes between 2004 and 2010 using the AROC database. Lower-limb amputee data were identified using AROC impairment codes 5.3 to 5.7 (Australasian Rehabilitation Outcome Centre 2007) (table 3.1). All data were de-identified before data extraction and analysis. Ethical approval for this study was provided by the Southern Adelaide Clinical Human Research Ethics Committee.

Table 3.1: Definition of AN-SNAP and impairment codes used for lower-limb amputees.

Term	Definition
AN-SNAP Code:	
S2–224	Functional Independence Measure Motor score 72–91
S2–225	Functional Independence Measure Motor score 14–71
Impairment Code:	
5.3	Unilateral amputation above knee or through the knee
5.4	Unilateral amputation below the knee
5.5	Bilateral amputation, both above knee or through knee
5.6	Bilateral amputation, one above or through knee, one below the knee
5.7	Bilateral amputation, both below the knee

3.3.2 AROC dataset

Australasian ROC was established in July 2002 as a joint initiative of the Australasian Rehabilitation sector and is funded by contributions from all stakeholders, including facilities, health funds, Department of Veterans' Affairs, health departments (state and commonwealth), some general insurers and the Australasian Faculty of Rehabilitation Medicine. Australasian ROC receives quarterly episodic data from private and public rehabilitation facilities across Australia. Thirty facilities were submitting data to AROC in 2002. However AROC

coverage grew steadily with 109 facilities submitting by 2004, and 180 by 2011, representing more than 95% of Australian rehabilitation facilities and inpatient episodes. Of the rehabilitation facilities submitting data to AROC, 21 units specialise in lower-limb amputee rehabilitation and contributed the majority of amputee episode data (59.3%). The AROC dataset includes 42 items: sociodemographic, funding and employment details, episode items (admission and discharge), medical (impairment codes, comorbidities, complications), and outcome data (patient level of function at admission and discharge) (Eagar et al. 1997; Green & Gordon 2007).

Data within the AROC database are classified under the AN-SNAP casemix classification system, which was developed at the University of Wollongong in 1997 (Eagar et al. 1997). The purpose of AN-SNAP was to provide a casemix classification system for sub and non-acute care provided in several treatment settings. It was borne out of a growing recognition that patients should be classified by functional ability, rather than by diagnosis and procedure codes as in the acute sector (Green & Gordon 2007). The AN-SNAP subdivides case episodes according to both diagnosis and functional level, using the FIM. Version 2 AN-SNAP classification became operational in 2007 (Green & Gordon 2007) and includes 45 inpatient rehabilitation classes. For amputees, AN-SNAP version 2 contains two functional levels based on the FIM motor (FIM (Mot)) score. The two functional classes are S2–224 (FIM Mot 72–91) and S2–225 (FIM Mot 14–71). Functional IM is an internationally recognised and reliable functional-status instrument that is widely used with rehabilitation inpatients (Dodds et al. 1993; Kidd et al. 1995; Ottenbacher et al. 1996; Stineman et al. 1996). It contains 18 items, 13 of which relate to motor function, and five to cognition. Total FIM scores including both

motor and cognitive aspects range from 18 to 126, with higher scores representing greater functionality. Functional IM scores relating to motor assessments range from 13 to 91. Australasian ROC holds a territory licence for use of the FIM in Australia and New Zealand, and is responsible for the national certification and training for all accredited rehabilitation clinicians. Clinical staff are required to be recredentialed in the FIM every 2 years to maximise the quality of data. All data received by AROC are screened for errors and missing data before adding the episodes to the database. If necessary, AROC will request that the submitting facility review and correct any inconsistencies.

3.3.3 Analysis

De-identified lower-limb amputee rehabilitation episodes between 2004 and 2010 were extracted from the main AROC database using AROC impairment codes 5.3–5.7 (Australasian Rehabilitation Outcome Centre 2007). Data were then transferred to SPSS version 19.0 for analysis. Descriptive analysis was conducted on demographics, FIM (Mot) (admission score, discharge score, change and efficiency), LOS, clinical characteristics and discharge destination collated by year, AN-SNAP classification, impairment code and States of Australia. Functional IM (Mot) change is the difference between admission and discharge FIM (Mot) scores, and is an indicator of change in functional status during rehabilitation stay. Functional IM (Mot) efficiency is the FIM (Mot) change achieved per day of LOS. Significant differences were analysed by independent sample *t*-tests and between-subjects analysis of variance (ANOVA) with post-hoc pairwise comparisons using Tukey adjustments for significant results. Results of descriptive analysis are presented as a

mean and 95% confidence interval (95% CI). Results of independent sample *t*-test and ANOVA are presented as mean difference and 95% CI.

3.4 Results

3.4.1 Episodes

A total of 6588 lower-limb amputee episodes were submitted to the AROC database between 2004 and 2010. However only 4864 (73.8%) of episodes could be analysed for rehabilitation outcomes, which requires valid LOS and valid FIM scores. Of all rehabilitation episodes submitted to the AROC database between 2004 and 2010, lower-limb amputees contributed only 1.7% of episodes (see table 3.2). Of all submitted amputee episode data, New South Wales (NSW) was the largest contributing state (48.5%), whilst the majority of episodes were submitted from public facilities (83.4%). The number of lower-limb amputee episodes submitted to the AROC database grew steadily each year as did the number of facilities submitting lower-limb amputee episodes data, reaching 99 by 2010.

Table 3.2: Episodes submitted to the AROC database from 2004 to 2010.

Impairment codes as per table 3.1

	Year							All
Impairment Code	2004	2005	2006	2007	2008	2009	2010	Years
5.3	193	252	242	264	248	294	260	1753
5.4	479	531	579	667	636	695	615	4202
5.5	12	19	21	21	23	17	26	139
5.6	28	32	31	15	32	26	24	188
5.7	40	47	45	53	45	47	29	306
All amputee episodes	752	881	918	1020	984	1079	954	6588
All rehabilitation episodes	37920	45338	50755	55393	60797	67306	75621	393130
% Amputee	2.0%	1.9%	1.8%	1.6%	1.6%	1.3%	1.3%	1.7%

3.4.2 Demographics

The majority of lower-limb amputee episodes were male (71.8%), with mean age of all episodes being 67.9 years (95% CI: 67.6–68.3). Episodes in the private sector had a mean age 6.1 years lower than those in the public sector (95% CI: 5.1–7.0, $p < 0.01$). Episodes categorised to the higher functioning AN-SNAP class (S2–224) had a lower mean age by 10.0 years than did those in S2–225 (95% CI: 9.2–10.8, $p < 0.001$). Year-on-year analysis revealed a trend for decreasing age, with the mean age in 2004 being 70.2 years (95% CI: 69.1–71.3), dropping in 2010 to 67.1 years (95% CI: 66.2–68.0).

3.4.3 Clinical characteristics

The majority (63.6%) of episodes within the AROC database were unilateral below-knee amputees, with most episodes being the lower functioning AN-SNAP classification, S2–225 (71.8%). Table 3.3 demonstrates this to be the case across all states of Australia. The majority of episodes were admitted from private residence (89.5%), with 87.1% of those admitted from private residence also returning there upon completion of rehabilitation.

Table 3.3: Variation in lower-limb amputee admissions (%) across impairment codes and AN-SNAP classifications by states of Australia.

Impairment codes as per table 3.1

	Impairment Code					AN-SNAP	
	5.3	5.4	5.5	5.6	5.7	S2–224	S2–225
NSW	653 (28)	1424 (60)	58 (2)	73 (3)	150 (6)	628 (27)	1714 (73)
Vic	180 (21)	602 (72)	7 (1)	16 (2)	36 (4)	154 (18)	685 (82)
Qld	203 (32)	383 (59)	21 (3)	16 (2)	21 (3)	196 (31)	443 (69)
SA	166 (28)	379 (65)	14 (2)	10 (2)	18 (3)	165 (28)	421 (72)
Other	108 (25)	306 (71)	2 (0)	12 (3)	6 (1)	186 (45)	228 (55)

NSW, New South Wales; Vic, Victoria; Qld, Queensland; SA, South Australia; Other, includes Tasmania, Western Australia, Northern Territory and Australian Capital Territory.

Complications and comorbidities occurring during rehabilitation were not well recorded in the dataset before 2007. In 2004, 94.7% of episodes did not record

complications during rehabilitation. This figure dropped to 51.1% in 2007, and by 2010 there were only 2.7% of episodes with missing data for complications during rehabilitation. Of submitted data where complications were recorded from 2007 to 2010, 44.2% reported at least one complication, commonly being a wound infection (33.3%) or a fall (12.5%). Of submitted comorbidities data between 2007 and 2010, 67.4% had at least one comorbidity, with 43.4% having multiple comorbidities. The most commonly reported comorbidity was diabetes mellitus (43.4%). Comorbidities and complications did not vary by year or impairment code. However, analysis by AN-SNAP classification revealed that episodes in S2–225 were significantly more likely to have at least one complication (45.8%) compared with those in S2–224 (31.2%) ($x^2(1) = 49.9$, $p < 0.001$). Episodes in S2–225 were also significantly more likely to have multiple comorbidities (36.2%) compared with those in S2–224 (27.4%) ($x^2(1) = 40.6$, $p < 0.001$).

Program suspension recording changed in 2007 to enable reporting of the number of suspensions, total number of days of the suspension period, and if the suspension was planned or not. Since 2007 38.1% of episodes reported a suspension to treatment during inpatient rehabilitation. Of those, only 17.1% reported the number of suspensions, 21.1% the length, and all reported if the suspension was planned. Of those episodes with only one suspension (75.4%), the mean length of suspension was 4.7 days (95% CI: 3.8 – 5.6). The program suspension was a planned occurrence in 49.1% of episodes.

3.4.4 Rehabilitation outcomes

Mean LOS for all lower-limb amputee episodes was 36.1 days (95% CI: 35.4–36.9). FIM (Mot) change was 13.5 (95% CI: 13.2–13.8) and FIM (Mot) efficiency was 0.5 (95% CI: 0.5–0.5). Year-on-year analysis (see table 3.4) revealed a trend for increasing LOS and FIM (Mot) change, however this did not reach significance. Table 3.5 provides results of rehabilitation outcomes from submitted episode data for lower-limb amputee impairment codes. Post-hoc analysis revealed that impairment code 5.5 had a significantly lower admission FIM (Mot) than did all other impairment codes. Impairment code 5.5 also had significantly lower discharge FIM (Mot) scores than did all other impairment codes, while impairment code 5.4 had significantly higher discharge FIM (Mot) scores than did all other impairment codes. Analysis by AN-SNAP classification revealed that LOS was longer for S2–225 at 40.6 days (95% CI: 39.8–41.5) than for S2–224 at 24.4 days (95%CI: 23.4–25.4), with a significant difference of 16.2 days (95% CI: 14.7–17.8, $p < 0.001$). FIM (mot) differences were also found between AN-SNAP classifications, with S2–225 achieving a higher FIM (mot) change of 16.8 (95%CI: 16.5–17.2) than the 4.8 (95%CI: 4.5–5.0) achieved for S2–224, with the mean difference of 12.0 reaching significance (95% CI: 11.5–12.6, $p < 0.001$). Functional IM (mot) efficiency was also found to be different between AN-SNAP classifications, with S2–225 being 0.6 (95%CI: 0.5–0.6) compared with 0.3 (95%CI: 0.3–0.3) for S2–224, and the mean difference of 0.3 reaching significance (95% CI: 0.2–0.3, $p < 0.001$). Analysis by states (see table 3.6) revealed significant variations in LOS, FIM (Mot) change and FIM (Mot) efficiency. Post-hoc analysis revealed NSW had shorter LOS than did either South Australia (SA) (by 3.7 days, 95% CI: 0.6–6.8, $p < 0.01$) or Victoria (Vic) (by 6.3 days, 95% CI: 3.7–9.0, $p < 0.001$), but Queensland (Qld) had

significantly shorter LOS than did Vic, by 4.4 days (95% CI: 0.9–7.9, $p < 0.01$). Vic achieved a significantly greater FIM (Mot) change than did Qld, by 1.6 points (95% CI: 0.1–3.1, $p < 0.05$). Functional IM (Mot) efficiency was significantly greater for NSW than for SA by 0.1 (95% CI: 0.0–0.2, $p < 0.05$) and for Vic by 0.1 (95% CI: 0.0–0.1, $p < 0.05$). Caution should however be taken when considering these results due to variations in organisation of rehabilitation and prosthetic services across Australia.

Table 3.4: Comparison of lower-limb amputee rehabilitation outcomes 2004–2010.

	2004 (*n* = 535)	2005 (*n* = 600)	2006 (*n* = 686)	2007 (*n* = 747)	2008 (*n* = 743)	2009 (*n* = 823)	2010 (*n* = 730)	Total (*n* = 4864)	*p* value*
LOS (95% CI)	33.4 (31.0–35.8)	34.2 (32.4–36.1)	35.4 (33.5–37.3)	34.8 (33.1–36.6)	34.6 (32.9–36.4)	38.1 (36.3–40.0)	39.1 (37.0–41.1)	36.1 (35.4–36.9)	0.0001
LOS casemix adjusted mean (95% CI)	-1.0 (-3.3-1.3)	-0.1 (-1.9-1.7)	-0.2 (-1.9–1.6)	0.1 (-1.6–1.9)	-0.9 (-2.6–0.7)	3.1 (1.3–4.8)	3.8 (1.8–5.8)	0.8 (0.1–1.5)	0.0001
Admission FIM Mot (95% CI)	61.1 (59.8–62.5)	61.4 (60.2–62.7)	60.3 (59.1–61.5)	61.5 (60.4–62.6)	60.8 (59.7–61.9)	59.6 (58.5–60.7)	59.1 (58.0–60.3)	60.1 (59.7–60.6)	0.018
Discharge FIM Mot (95% CI)	73.8 (72.7–75.0)	75.1 (74.1–76.1)	73.7 (72.7–74.7)	74.9 (74.1–75.8)	73.7 (72.8–74.6)	73.6 (72.6–74.5)	74.0 (73.0–75.0)	73.6 (73.3–74.0)	0.101
FIM Mot change (95% CI)	12.7 (11.8–13.6)	13.6 (12.8–14.5)	13.4 (12.5–14.2)	13.4 (12.6–14.2)	12.9 (12.1–13.6)	14.0 (13.2–14.7)	14.9 (14.0–15.7)	13.5 (13.2–13.8)	0.001
FIM Mot efficiency (95% CI)	0.5 (0.4–0.5)	0.5 (0.5–0.6)	0.5 (0.4–0.5)	0.5 (0.5–0.6)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.540
FIM casemix adjusted mean (95% CI)	-1.5 (-2.3–-0.6)	-0.6 (-1.4–0.3)	-0.9 (-1.7– -0.1)	-0.6 (-1.4–0.2)	-1.8 (-2.5– -1.1)	-0.5 (-1.3–0.3)	0.3 (-0.5–1.1)	-0.8 (-1.1– -0.5)	0.007
Discharge to private residence *n* (%)	144 (73)	348 (81)	480 (81)	596 (84)	611 (86)	648 (83)	603 (86)	3430 (83)	0.0001
Sector: private n (%) public *n* (%)	122 (23) 413 (77)	125 (21) 475 (79)	91 (13) 595 (87)	123 (16) 624 (84)	119 (16) 624 (84)	127 (15) 696 (85)	100 (14) 630 (86)	807 (17) 4057 (83)	0.0001

*Excluding 'Total' in analysis. LOS, length of stay; FIM, Functional Independence Measure; FIM Mot, motor score of the Functional Independence Measure

Table 3.5: Comparison of lower-limb amputee rehabilitation outcomes by impairment code.

Impairment codes as per table 3.1

	5.3 (*n* = 1310)	5.4 (*n* = 3094)	5.5 (*n* = 102)	5.6 (*n* = 127)	5.7 (*n* = 231)	*p* value
LOS (95% CI)	35.7 (34.3–37.1)	36.3 (35.4–37.2)	39.3 (33.1–45.5)	31.3 (27.2–35.4)	37.8 (34.1–41.6)	0.110
Admission FIM Mot (95% CI)	59.0 (58.1–59.9)	61.2 (60.7–61.8)	49.4 (45.8–53.0)	58.5 (55.4–61.7)	56.7 (54.6–58.9)	0.0001
Discharge FIM Mot (95% CI)	72.4 (71.7–73.2)	74.8 (74.4–75.3)	64.6 (61.0–68.2)	70.3 (67.7–72.9)	70.1 (68.0–72.2)	0.0001
FIM Mot change (95% CI)	13.4 (12.8–14.0)	13.6 (13.2–14.0)	15.2 (12.8–17.7)	11.7 (9.9–13.6)	13.4 (11.7–15.0)	0.181
FIM Mot efficiency (95% CI)	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.6 (0.4–0.7)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.764
Discharge to private residence *n* (%)	889 (81)	2256 (85)	59 (74)	78 (79)	148 (79)	0.001
Sector: private n (%)	244 (19)	497 (16)	19 (19)	14 (11)	33 (14)	0.073
public *n* (%)	1066 (81)	2597 (84)	83 (81)	113 (89)	198 (86)	

LOS, length of stay; FIM, Functional Independence Measure; FIM Mot, motor score of the Functional Independence Measure

Table 3.6: Comparison of lower-limb amputee rehabilitation outcomes by states of Australia.

	NSW (*n* = 2358)	Vic (*n* = 841)	Qld (*n* = 644)	SA (*n* = 587)	Other (*n* = 434)	*p* value*
LOS (95% CI)	34.3 (33.3–35.3)	40.7 (38.9–42.4)	36.3 (34.0–38.6)	38.1 (36.0–40.2)	34.3 (32.1–36.5)	0.0001
Admission FIM Mot (95% CI)	59.3 (58.6–59.9)	58.6 (57.6–59.5)	60.2 (59.0–61.4)	60.8 (59.7–62.0)	66.9 (65.6–68.2)	0.029
Discharge FIM Mot (95% CI)	73.0 (72.4–73.6)	73.1 (72.3–73.9)	73.1 (72.1–74.1)	74.3 (73.3–75.2)	78.3 (77.4–79.2)	0.223
FIM Mot change (95% CI)	13.7 (13.3–14.2)	14.5 (13.8–15.3)	12.9 (12.1–13.7)	13.4 (12.6–14.2)	11.4 (10.3–12.4)	0.036
FIM Mot efficiency (95% CI)	0.5 (0.5–0.6)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.4 (0.4–0.5)	0.5 (0.4–0.5)	0.002
Discharge to private residence *n* (%)	1506 (81)	642 (83)	514 (85)	422 (89)	346 (84)	0.0001
Sector: private *n* (%)	364 (15)	40 (5)	333 (52)	16 (3)	54 (12)	0.0001
public *n* (%)	1994 (85)	801 (95)	311 (48)	571 (97)	380 (88)	

*Excluding 'Other' in analysis. NSW, New South Wales; Vic, Victoria; Qld, Queensland; SA, South Australia; LOS, length of stay; FIM, Functional Independence Measure; FIM Mot, motor score of the Functional Independence Measure.

3.5 Discussion

The AROC dataset proved useful for providing a snapshot of lower-limb amputee rehabilitation nationally. Since inception of the database, several modifications and improvements have been implemented to ensure that data recording is correct and accurate and provides a realistic picture of the current state of rehabilitation. For lower-limb amputees, an adjunct dataset was introduced to specifically target outcomes related to amputees. Once sufficient data has been collected, the addition of the adjunct dataset should allow a more comprehensive analysis of amputee rehabilitation. In the meantime, results from the current version of the AROC database indicate that the majority of cases were managed by the public sector, and unilateral below-knee episodes were the most common in this database, which is typically the case in amputee rehabilitation facilities (Lim et al. 2006; Wu, Chan & Bowring 2010). Overall LOS can also be considered to be quite long compared with other patient populations including stroke (27 days) and orthopaedic fractures (23 days) (Simmonds & Stevermuer 2007; Simmonds & Stevermuer 2008), and amputees entering rehabilitation facilities can be considered old. The significant LOS may be attributed to several factors such as waiting for suitable wound healing to occur before prosthetic casting, waiting for adequate home modifications to be made so that the amputee may safely return home, or the earlier arrival of amputees from acute setting to rehabilitation facilities.

Year-on-year analysis revealed a trend for increasing LOS, FIM (Mot) change and decreasing age. As discharge to private residence has remained relatively steady over the observation period, it appears that the lower admission FIM (Mot) scores entering

rehabilitation may contribute to the longer LOS to achieve a greater FIM (Mot) change and ensure similar discharge FIM (Mot) scores. Increasing LOS in this population appears to be contradictory to other rehabilitation patient populations who are typically experiencing decreasing rehabilitation LOS (Simmonds & Stevermuer 2007; Simmonds & Stevermuer 2008). The decreasing age observed may be related to the increasing prevalence of diabetes mellitus in younger adults due to the increasing incidence of obesity and physical inactivity (Eckel, Grundy & Zimmet 2005; Hu 2011; Wild et al. 2004). However several other factors may also have contributed, such as rehabilitation facilities admitting older amputees for transfer training only under reconditioning (rather than rehabilitation), or facilities not admitting older amputees from care facilities for rehabilitation as their care is already maximal.

The trend of increasing LOS and decreasing age should raise concerns within the wider amputee rehabilitation community. Clinicians and public health physicians may need to review current rehabilitation practice and pursue service delivery modifications aimed at reducing LOS and promoting good rehabilitation outcomes. To assist in the review of current rehabilitation practice, clinicians should ensure active data collection of all items within the AROC amputee adjunct dataset, to provide a comprehensive overview of lower-limb amputee rehabilitation in Australia. Attention should be directed towards the increasing LOS to determine if improved services, such as early identification and implementation of home modifications, may assist in reducing LOS. Service delivery modifications may also need to be considered and may include earlier admittance to rehabilitation facilities to ensure rehabilitation begins as soon as possible.

Discrimination of episodes by AN-SNAP classification through use of the FIM appears to be an effective method of distinguishing functional abilities and rehabilitation outcomes of lower-limb amputees. Significant differences were found in LOS, FIM (Mot) change and efficiency between classifications. Potential exists for AN-SNAP classes to be used more effectively in planning and targeting rehabilitation programs for the lower-limb amputee population and may be a useful service-modification option to assist in the reduction of LOS. Although the FIM itself is not an amputee-specific tool, it is a widely used and useful tool for obtaining a broad snapshot of a patient's potential and allows comparison of amputees with other patient populations. Australasian ROC has recently introduced an amputee adjunct dataset which will provide more specific amputee-related rehabilitation outcomes. Although insufficient data are currently available for analysis, the addition of this adjunct dataset will prove useful for investigating amputee rehabilitation nationally.

There are limitations of this study to acknowledge. Outcomes from this study rely upon the quality of data recorded within the database. Data within this database are recorded at various rehabilitation facilities by a wide variety of clinical staff throughout Australia. To help ensure quality of data submitted to the AROC database, clinical staff undergo regular training. Data submitted to AROC are checked for validity and returned for correction if required. Not all Australian rehabilitation facilities submit episode data to the AROC database. Currently 180 facilities submit data to AROC, and this represents more than 95% of rehabilitation facilities in Australia. However, that number has not remained constant over the

observation period with the number of submitting facilities growing over time. Although interesting, there are limitations in reporting outcomes by states of Australia. Whilst there were variations in rehabilitation outcomes across Australia, results also indicated variations in episodes discriminated by AN-SNAP, and impairment codes exist that may have contributed to this (see table 3.3). However, there may be other factors influencing the variation in rehabilitation outcomes across Australia. These factors may include the variation in funding structures and organisations of rehabilitation and prosthetic facilities across Australia. This study is also unable to detail the variation in amputee clinical practice across Australia that would impact rehabilitation outcomes. Finally, some amputee-specific items should be addressed to provide a clearer picture of the state of amputee rehabilitation. Although admission and discharge FIM scores are provided, information regarding level of function before amputation is lacking. Factors such as mobility before amputation are known to affect the ability of amputees to achieve successful rehabilitation with a prosthesis (Sansam et al. 2009). Inclusion of additional outcomes may prove useful in describing rehabilitation and functional outcomes of amputees.

3.6 Conclusion

Although only a small proportion of all episodes in the AROC database, this subset of lower-limb amputee episodes has provided a useful snapshot of the current state of amputee rehabilitation in Australia. Mean age of amputees was 67.9 years with a trend for decreasing age over the observation period. Overall LOS of this amputee subset was considered high in comparison to other patient populations. However, unlike other patient populations there does not appear to be a trend for decreasing

LOS. The AN-SNAP classes appear effective in distinguishing rehabilitation outcomes, and could potentially be used more effectively in planning rehabilitation programs.

CHAPTER FOUR: PHYSIOTHERAPY REHABILITATION FOR INDIVIDUALS WITH LOWER-LIMB AMPUTATION: A 15 YEAR CLINICAL SERIES

About this chapter:

The purpose of this chapter was to identify challenges facing amputee rehabilitation in Australia. In contrast to the previous chapter, this chapter uses a clinical dataset maintained by one service over many years and provides more information of clinical variables. This study reported demographics, clinical characteristics and time to key rehabilitation outcomes for amputees admitted to one metropolitan prosthetic rehabilitation service where participants were recruited from for latter studies in this thesis. Analysis was conducted to determine how these characteristics changed over the period of observation. This chapter specifically addressed the research question 'What outcomes are currently achieved by amputee rehabilitation units in Australia?'. The results in this chapter were published in *Physiotherapy Research International.*

4.1 Abstract

Individuals with amputations are a core group of patients in Australian rehabilitation units who have a long index LOS. The Repatriation General Hospital offers general rehabilitation services to the population of Southern Adelaide (population 350,000) and includes an on-site prosthetic manufacturing facility. Using a physiotherapy database at the Repatriation General Hospital, the following questions were investigated: What are the demographic and clinical characteristics of patients admitted for lower-limb prosthetic rehabilitation over 15 years? What are the times to rehabilitation outcomes? How have these changed over 15 years with changes in service delivery? A retrospective observational study using a physiotherapy clinical database (1996-2010) of 531 consecutive individuals with lower-limb amputation at one South Australian hospital (Repatriation General Hospital). Two changes in service delivery: (1) A multidisciplinary interim prosthetic program (IPP) introduced in 1998, and (2) removable rigid dressings (RRDs) introduced in 2000. Outcome measures were patient demographics, clinical characteristics and time to rehabilitation outcome markers. Mean age was 68 years (standard deviation (SD) 15) with 69% male, 80% vascular and 68% transtibial. The overall median inpatient rehabilitation length of stay was 39 days (IQR 26-57). Individuals with amputation entering rehabilitation each year had a higher number of comorbidities (β: 0.08; 95% CI: 0.05-0.11). Introduction of the IPP was associated with a significant reduction in time to initial prosthetic casting, independent walk and inpatient Rehabilitation LOS. Introduction of RRDs was associated with a significant reduction in time to wound healing, initial prosthetic casting and independent walk. Individuals with amputation were typically elderly, vascular, males with transtibial amputations. Introduction of

the IPP and RRDs successfully reduced time to rehabilitation outcomes including independent walk; an outcome which is rarely reported but is of significance to patients and physiotherapists.

4.2 Introduction

Improvements in amputee outcomes have occurred as a result of medical and surgical innovations, but amputation numbers remain high and rehabilitation of individuals with amputation continues to be a core business for medical rehabilitation units across the world. Most individuals with lower-limb amputation in the developed world are elderly, vascular patients, often presenting with diabetes mellitus (DM) (Nehler et al. 2003; Pernot et al. 2000; Stone et al. 2007). According to the Australian Institute of Health and Welfare (2008), it is estimated that 700,000 Australians (3.6% population) were diagnosed with diabetes mellitus and 3,394 diabetic related lower-limb amputations were performed in Australia in 2004-05.

Individuals with amputation are a core group in Australian rehabilitation units who have a long index LOS. The long LOS associated with the index admission is justified by clinicians as important because restoring independent mobility and community integration reduces the larger social and health service costs associated with disability. It is widely believed that growth of interventional vascular surgery has helped reduce lower-limb amputation numbers in vascular patients (Feinglass et al. 1999; Nowygrod et al. 2006). However, it is unknown whether the demographics of individuals with amputation entering rehabilitation units now have changed. This may result in a change in the outcomes achieved, time taken to achieve these outcomes or in the nature of the clinical programs provided by physiotherapists. National outcome data collected by AROC suggests there are wide variations in physiotherapy practice across Australia but at this stage information on clinical practice is lacking (Australasian Rehabilitation Outcome Centre 2010).

Data from amputee rehabilitation hospital cohorts in Australia is limited. Six studies were identified (Hubbard 1989; Jones 1990b; Jones, Hall & Schuld 1993; Katrak & Baggott 1980; Lim et al. 2006; Wu, Chan & Bowring 2010) with all reporting demographics and clinical characteristics of the cohorts. However, only inpatient rehabilitation LOS was reported as an outcome and the identified studies failed to investigate other rehabilitation outcomes such as times to wound healing, initial prosthetic casting and independent walk. Successful wound healing is an important rehabilitation marker as it allows rehabilitation with a physiotherapist to progress towards mobilising with a prosthesis. Reported times from amputation to initial prosthetic casting vary, ranging from 36.4 days (IQR 24-50) with soft dressings (Taylor et al. 2008) to 23.3 days (SD 19.5) with RRDs (Deutsch et al. 2005). In a recent review it was reported that 56-97% of individuals with amputation regain the ability to walk (Van Velzen et al. 2006), however time to independent walk is rarely reported in the literature. Independent walking with a prosthesis remains the key outcome for a physiotherapist in an amputee rehabilitation service as it allows patients to work towards achieving independence and will likely contribute to improved quality of life (Hamamura et al. 2009; Pell et al. 1993).

The Repatriation General Hospital offers general rehabilitation services to the population of Southern Adelaide (population 350,000) and includes an on-site prosthetic manufacturing facility. Individuals with lower-limb amputation attend a multidisciplinary gym session with a dedicated amputee physiotherapist and prosthetist. Six sessions are conducted per week in a group setting. Sessions include upper- and lower-limb strengthening, prosthetic fitting and modification, balance and

gait re-education. Physiotherapy forms only part of the multidisciplinary rehabilitation service offered to individuals with amputation at the Repatriation General Hospital. Other services are provided by rehabilitation medical consultants, rehabilitation nursing, occupational therapy (for home modifications, return to driving and return to work), social work, psychology services (if required) and dietetics (if required). During the period of observation, two significant changes in service delivery occurred. In 1998 an interim prosthetic program was implemented which resulted in streamlined multidisciplinary services, and provided patients with an interim prosthesis which incorporated a laminated prosthetic socket with modular componentry (made by a prosthetist) (see figure 4.1). No interim prosthesis was used prior to this and gait retraining was achieved with an air bag system (pneumatic post amputation mobility aid) for transtibial, knee disarticulation and transfemoral patients. Routine fitting of RRDs was introduced in 2000 (fitted by a prosthetist) for individuals with transtibial amputation (current practice dictates that individuals with transfemoral amputation are not managed with RRDs). Fitting occurred immediately post operatively or within 24 hours. The evidence supporting RRDs indicates a reduction in; oedema (Mueller 1982; Nawijn et al. 2005), time from amputation to wound healing (Deutsch et al. 2005; Nawijn et al. 2005) time from amputation to initial prosthetic casting (Hughes, Ni & Wilson 1998; Taylor et al. 2008; Woodburn et al. 2004; Wu, Keagy & Krick 1979) and rehabilitation LOS (Taylor et al. 2008).

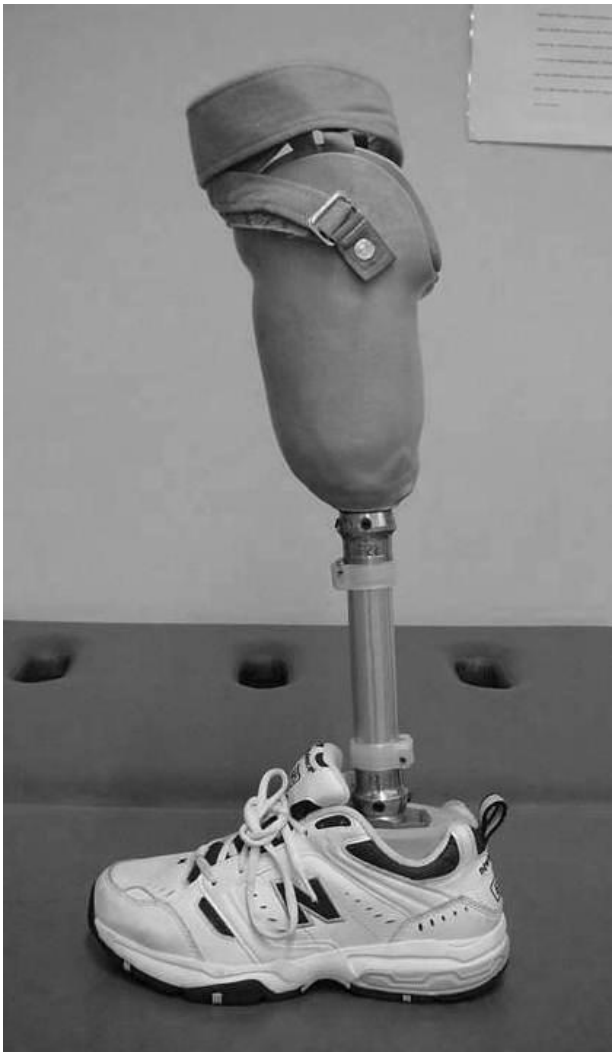

Figure 4.1: An interim prosthesis with fully laminated prosthetic socket and modular componentry.

Using a physiotherapy database of patients who received rehabilitation for a lower-limb amputation between 1st January 1996 and 31st December 2010 at the Repatriation General Hospital, following questions were investigated:

1. What are the demographics and clinical characteristics of individuals with lower-limb amputation admitted for rehabilitation and how have these changed over the observation period?
2. What are the times to rehabilitation outcomes (wound healing, initial

prosthetic casting, independent walk and inpatient rehabilitation LOS)?

3. How have demographics, clinical characteristics and the changing model of rehabilitation services offered at the Repatriation General Hospital affected rehabilitation outcomes?

4.3 Methods

4.3.1 Design

This study was a retrospective audit of a clinical physiotherapy database of consecutive individuals with lower-limb amputation admitted for prosthetic rehabilitation at the Repatriation General Hospital between January 1st 1996 and December 31st 2010. The period 1996 to 2010 marks the beginning of inpatient amputee rehabilitation at the Repatriation General Hospital to the most recent completed year of data at time of writing. Records were examined and data extracted for analysis. Extracted data included demographics, clinical characteristics and rehabilitation outcomes. Ethical approval was provided by the Southern Adelaide Flinders Clinical Human Research Ethics Committee.

4.3.2 Subjects

The Repatriation General Hospital provides inpatient and outpatient prosthetic rehabilitation for individuals with major lower-limb amputation. Amputation types included were transtibial, transfemoral, knee disarticulation, hip disarticulation, unilateral and bilateral. Acute amputation services were provided by both the Repatriation General Hospital, and hospitals which are geographically separate to the Repatriation General Hospital.

4.3.3 Outcome measures

The primary rehabilitation outcome markers were; wound healing, initial prosthetic casting, independent walk and inpatient rehabilitation LOS. A secondary measure of total rehabilitation program duration (RPD) was also reported. Wound healing was determined from visual inspection by the amputee physiotherapist and prosthetist, and confirmed with the rehabilitation medical consultant. Independent walking was determined by the amputee physiotherapist when the patient could mobilise 10 metres independently (with or without gait aid). Inpatient rehabilitation LOS was defined as the timeframe from when an individual with amputation was admitted to the Repatriation General Hospital as an inpatient for prosthetic rehabilitation, to discharge from the Repatriation General Hospital. Total RPD included inpatient rehabilitation LOS and rehabilitation conducted as an outpatient. 'Length of stay' in hospitals is an outcome measure which can be difficult to interpret. While in some health systems it may be a surrogate for morbidity, in other systems it may represent patient preference, insurance company requirements or a lack of ambulatory alternatives (La Cour, Brok & Gøtzsche 2010). In this study 'length of stay' was used as a surrogate for morbidity, lack of ambulatory alternatives (i.e. inability to further progress mobility of the patient), lack of discharge destination preparation (i.e. delays in home modifications) and patient preference (home or hospital based rehabilitation). Insurance company requirements did not equally apply as a surrogate of rehabilitation LOS to this dataset. This is due to the Repatriation General Hospital being a publically funded hospital. Rehabilitation outcome markers were recorded in days post amputation and days post beginning rehabilitation. Information on patient demographics and clinical characteristics including age, gender, indication for

amputation, level of amputation, complications, comorbidities and discharge destination was also collected.

4.3.4 Data analysis

Regression analysis was conducted to model the age, total number of comorbidities and admission numbers of individuals with amputation entering rehabilitation over the 15 year observation period. Results are reported with a regression coefficient (β) with 95% confidence interval (CI). Logistic regression analysis was used to model discharge destinations and results are reported with an odds ratio (OR) with 95% CI. Zero truncated negative binomial regression was used to model times to wound healing, initial prosthetic casting, independent walk and inpatient rehabilitation LOS. Observations from patients who did not realise a particular rehabilitation outcome were excluded from the analysis. Zero truncated negative binomial regression accounts for over dispersion and the fact that all outcomes are counts greater than zero. Results are reported as an incidence rate ratio (IRR) with 95% CI. An IRR is a ratio which describes the relative rates of experiencing an outcome given an exposure. All multivariable models were adjusted for covariates as footnoted in the table. Models were fitted with terms in polynomial time up to the third power as appropriate in order to explain variation over the period of the study. A p-value of 0.05 (two-tailed) was considered statistically significant. All analyses were performed using Stata 11.2 for Windows (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.).

4.4 Results

4.4.1 Outcome of patients through rehabilitation

A total of 531 consecutive individuals with amputation were admitted for prosthetic rehabilitation at the Repatriation General Hospital between 1996 and 2010. Figure 4.2 presents the flow of patients through to the completion of rehabilitation. No significant difference was found in admission numbers per year over the observation period (β: 0.63; 95% CI: -0.34-1.61).

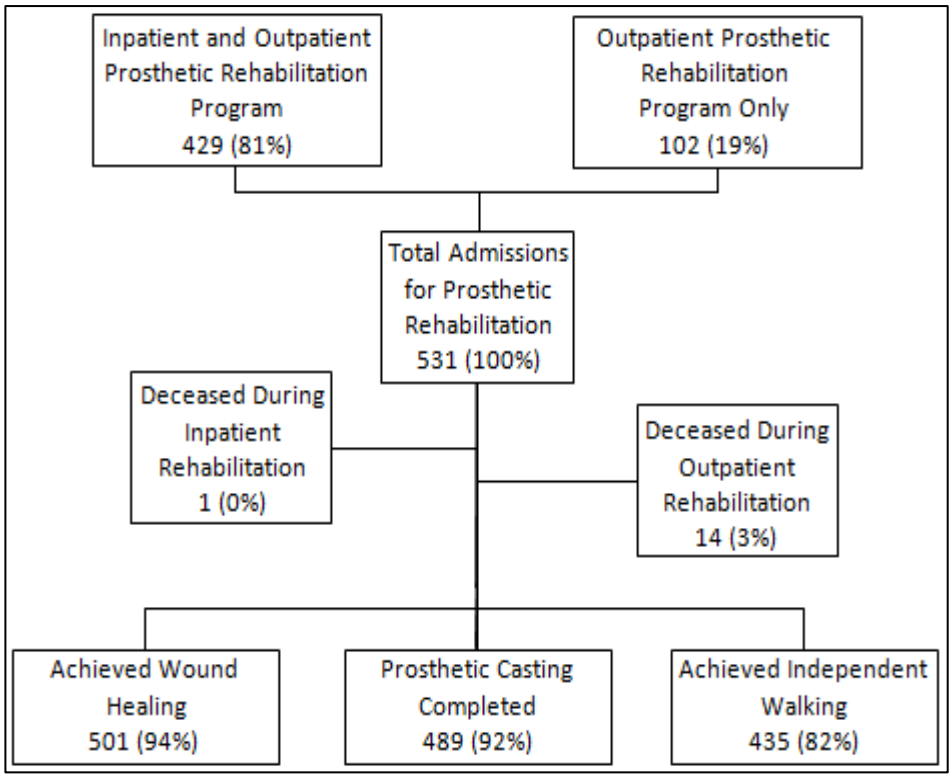

Figure 4.2: Outcome of cohort of individuals with lower-limb amputation admitted for rehabilitation at the Repatriation General Hospital between 1996-2010.

4.4.2 Patient demographics and clinical characteristics

Table 4.1 summarises patient demographics and clinical characteristics. Results indicate that age significantly decreased across the observation period (β: 0.49; 95% CI: 0.20-0.79), whilst total number of comorbidities increased across the observation period (β: 0.08; 95% CI: 0.05-0.11) (see table 4.2). The number of individuals with amputation discharged home also decreased across the observation period (OR: 0.92; 95% CI: 0.86-0.99) (see table 4.2). From 1996 to 2003, 8 patients were re-admitted to hospital, whilst from 2004 to 2010, 41 patients were re-admitted to hospital.

Table 4.1: Mean (SD) or n (%) of patient demographics and clinical characteristics.

Clinical Characteristics	Participants (n = 531)
Age (years)	68 (SD 15)
Gender	
Male	367 (69%)
Female	164 (31%)
Indication	426 (80%)
Vascular	250 (59%)
Vascular with diabetes	44 (8%)
Trauma	15 (3%)
Tumour	22 (4%)
Infection	24 (5%)
Other	
Type	
Transtibial	361 (68%)
Transfemoral	116 (22%)
Knee disarticulation	4 (1%)
Hip disarticulation	6 (1%)
Bilateral trans-tibial	29 (5%)
Bilateral trans-femoral	3 (1%)
Bilateral trans tib/fem	12 (2%)
Discharge Destination	
Home	327 (76%)
Transitional care	19 (4%)
Hospital	49 (11%)
Hostel	21 (5%)
Nursing home	12 (3%)
Deceased	1 (0%)
Comorbidities	
Peripheral vascular disease	329 (62%)
Diabetes mellitus	261 (49%)
Interstitial heart disease	163 (31%)
Osteoarthritis	43 (8%)
Hypertension	143 (27%)
Chronic renal failure	52 (10%)
Previous amputation	49 (9%)

Table 4.2: Number of admissions, mean (SD) age of patients, mean (SD) number of comorbidities and discharge home (%) each year of observation.

Year	Admissions (n)	Age (years)	Comorbidities (n)	Discharge Home (%)
1996	38	69.7 (13.1)	2.3 (1.0)	81
1997	25	70.2 (9.5)	2.5 (1.4)	77
1998	21	70.7 (14.5)	2.2 (1.4)	91
1999	35	73.6 (10.5)	2.8 (1.3)	92
2000	33	70.4 (13.1)	2.5 (1.2)	79
2001	35	71.1 (13.9)	3.0 (1.8)	65
2002	26	73.0 (11.7)	3.0 (1.6)	88
2003	49	67.6 (17.3)	3.4 (1.8)	80
2004	49	66.6 (19.1)	2.9 (1.6)	69
2005	35	67.2 (17.2)	3.3 (1.7)	80
2006	43	68.9 (12.6)	3.2 (1.8)	71
2007	33	66.2 (16.1)	3.5 (1.9)	67
2008	37	64.4 (12.9)	3.4 (2.0)	77
2009	36	65.8 (16.5)	3.4 (1.8)	64
2010	36	65.1 (13.9)	3.3 (1.7)	91

4.4.3 Rehabilitation outcomes

Figure 4.2 presents results of rehabilitation outcomes of the 531 patients admitted for prosthetic rehabilitation at the Repatriation General Hospital. Time to rehabilitation outcomes at the beginning (1996) and end (2010) of the observation period are presented in table 4.3.

Table 4.3: Median (IQR) for rehabilitation outcomes in days post amputation and days post beginning rehabilitation.

	Days Post Amputation			Rehabilitation Days		
Year (Admissions)	1996 (38)	2010 (36)	All (531)	1996 (38)	2010 (36)	All (531)
Outcome Marker						
Start Physiotherapy	46 (36-70)	14.5 (8-27)	15 (9-38)	N/A	N/A	N/A
Wound Healing	51 (36-79)	25 (21-35)	27 (22-54)	1 (1-1)	11 (1-14)	10 (1-17)
Prosthetic Casting	62.5 (44-80)	34 (27-62)	31.5 (24-60)	9 (4-20)	22 (15-28)	14 (8-22)
Independent Walk	105 (66-150)	61 (43-93)	68 (48-110)	30 (22-78)	47 (31–77)	45 (29-71)
Inpatient Rehabilitation LOS	N/A	N/A	N/A	34.5 (21.5-48.5)	43 (33-57)	39 (26-57)
Total RPD	147.5 (111- 225)	124 (70-154)	133 (93-198)	84 (57–136)	103.5(58-135)	106 (65-155)

LOS, length of stay; RPD, rehabilitation program duration.

4.4.4 Effect of demographics, clinical characteristics and the changing model of rehabilitation services on rehabilitation outcomes

Results for the rehabilitation outcomes wound healing, initial prosthetic casting, independent walk and inpatient rehabilitation LOS are presented in figures 4.3 and 4.4. Multivariable predictors of times to wound healing, initial prosthetic casting, independent walk and inpatient rehabilitation LOS are summarised in table 4.4. The introduction of the IPP was associated with a significant reduction in time to cast (IRR: 0.64; 95% CI: 0.56-0.72), independent walk (IRR: 0.80; 95% CI: 0.73-0.87) and inpatient rehabilitation LOS (IRR: 0.49; 95% CI: 0.30-0.79). Introduction of RRDs (applied to transtibial amputees only) was associated with a significant reduction in time to wound healing (IRR: 0.33; 95% CI: 0.27-0.40), prosthetic casting (IRR: 0.65; 95% CI: 0.57-0.73) and independent walk (IRR: 0.87; 95% CI: 0.76-1.00).

Table 4.4: Predictors of rehabilitation outcome measures.

	Wound Healing	Initial Prosthetic Casting	Independent Walk	Inpatient Rehabilitation LOS
	Multivariable	Multivariable	Multivariable	Multivariable
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Time				
1996 (ref)	1.00	1.00	1.00	1.00
2002	0.39 (0.12, 1.31)	1.15 (0.98, 1.36)	**1.19 (1.11, 1.27)*** **	**5.03 (2.22, 11.41)*** **
2010	0.39 (0.12, 1.31)	1.40 (0.96, 2.03)	**1.50 (1.13, 1.87)*** **	**4.46 (2.06, 9.68)*** **
IPP~	1.22 (0.69, 2.17)	**0.64 (0.56, 0.72)*** **	**0.80 (0.73, 0.87)** **	**0.49 (0.30, 0.79)** **
RRD #	**0.33 (0.27, 0.40)*** **	**0.65 (0.57, 0.73)*** **	**0.87 (0.76, 1.00)***	1.15 (0.97, 1.36)
Age	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	**1.01 (1.01, 1.02)*** **	**-**
1996	-	-	-	**1.03 (1.02, 1.04)*** **
2002	-	-	-	**1.02 (1.01, 1.02)*** **
2010	-	-	-	1.00 (0.99, 1.00)
Gender				
Male (ref)	1.00	1.00	1.00	1.00

Female	**1.18 (1.03, 1.36)***	1.07 (1.00, 1.15)	1.07 (0.99, 1.16)	1.06 (0.94, 1.19)
Amputation type				
Transtibial (ref)	1.00	1.00	1.00	1.00
Transfemoral	**0.68 (0.56, 0.82)*****	1.06 (0.86, 1.26)	**1.16 (1.07, 1.27)*****	**0.85 (0.75, 0.97)***
Bilateral	0.96 (0.75, 1.23)	1.13 (1.00, 1.27)	**1.33 (1.17, 1.50)*****	1.16 (0.95, 1.41)
Cause				
Vascular (ref)	1.00	1.00	1.00	1.00
Vascular DM	0.95 (0.63, 1.43)	1.01 (0.82, 1.25)	0.96 (0.77, 1.18)	0.95 (0.67, 1.34)
Trauma	0.83 (0.61, 1.14)	0.90 (0.76, 1.07)	0.94 (0.79, 1.11)	0.99 (0.75, 1.31)
Tumour	1.02 (0.62, 1.66)	0.85 (0.65, 1.11)	1.07 (0.84, 1.40)	1.11 (0.73, 1.70)
Infection	0.69 (0.48, 1.00)	**0.74 (0.60, 0.93)***	1.04 (0.84, 1.29)	0.87 (0.65, 1.17)
Other	0.88 (0.62, 1.26)	**0.76 (0.60, 0.95)***	1.07 (0.88, 1.29)	0.94 (0.71, 1.26)
Comorbidities				
IHD	**0.71 (0.57, 0.89)****	0.99 (0.91, 1.07)	1.04 (0.96, 1.14)	0.94 (0.82, 1.07)
PVD	0.96 (0.81, 1.14)	0.99 (0.90, 1.08)	0.96 (0.87, 1.06)	0.93 (0.79, 1.08)
DM	0.96 (0.65, 1.41)	0.82 (0.67, 1.01)	1.04 (0.86, 1.27)	1.00 (0.74, 1.36)
Complications				
Wound Breakdown	**1.59 (1.30, 1.93)*****	1.26 (1.05, 1.52)	**1.17 (1.02, 1.33)***	**1.31 (1.11, 1.54)****
Transtibial	-	-	1.14 (1.00, 1.31)	-
Transfemoral	-	-	**1.47 (1.24, 1.76)*****	-
Bilateral	-	-	**1.90 (1.39, 2.60)*****	-

Other Illness	0.91 (0.70, 1.17)	**1.10 (1.00, 1.20)***	**1.30 (1.17, 1.43)*****	**1.19 (1.01, 1.41)***
Stump skin problem	0.89 (0.73, 1.09)	0.97 (0.87, 1.07)	**1.21 (1.09, 1.35)*****	1.01 (0.85, 1.20)
Fall	1.20 (0.74, 1.95)	0.99 (0.86, 1.14)	1.08 (0.93, 1.26)	-
40 years old	-	-	-	**2.33 (1.23, 4.41)****
65 years old	-	-	-	**1.35 (1.06, 1.71)***
90 years old	-	-	-	0.93 (0.64, 1.37)
Medically Unstable	0.74 (0.39, 1.45)	0.93 (0.64, 1.34)	1.40 (0.70, 2.80)	1.63 (0.63, 4.22)
Problem other foot	0.89 (0.69, 1.13)	1.02 (0.90, 1.15)	1.21 (1.05, 1.39)	-
1996	-	-	-	**0.58 (0.36, 0.94)***
2002	-	-	-	0.85 (0.66, 1.10)
2010	-	-	-	1.42 (1.01, 1.99)
Stump pain	-	-	0.87 (0.64, 1.17)	1.21 (0.77, 1.92)

Each variable adjusted for all other co variables in table

IPP, interim prosthetic program; RRD, removable rigid dressing; DM, diabetes mellitus; IHD, interstitial heart disease; PVD, peripheral vascular disease.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

~ IPP introduced in 1998, # RRD introduced in 2000

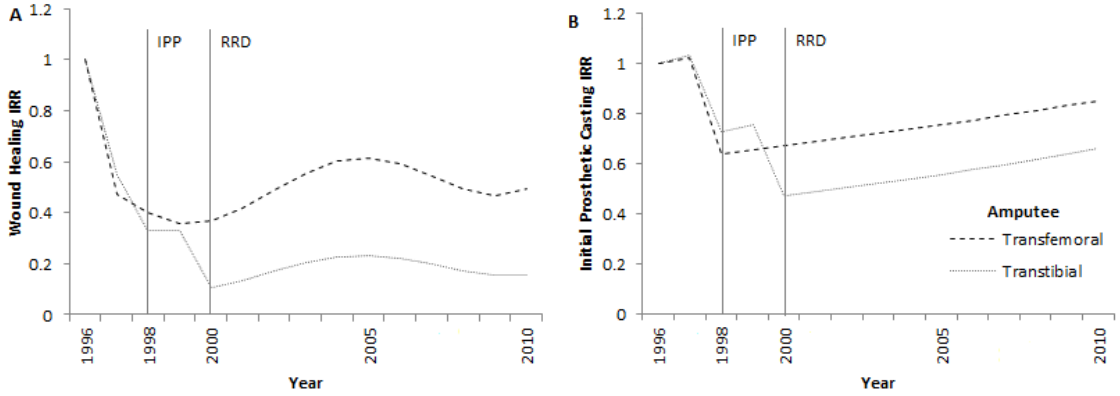

Figure 4.3: Change in IRR across the observation period for wound healing and initial prosthetic cast.

Time to wound healing (A) and time to initial prosthetic casting (B) for individuals with transtibial and transfemoral amputation of any age or indication for amputation with no comorbidities or complications.

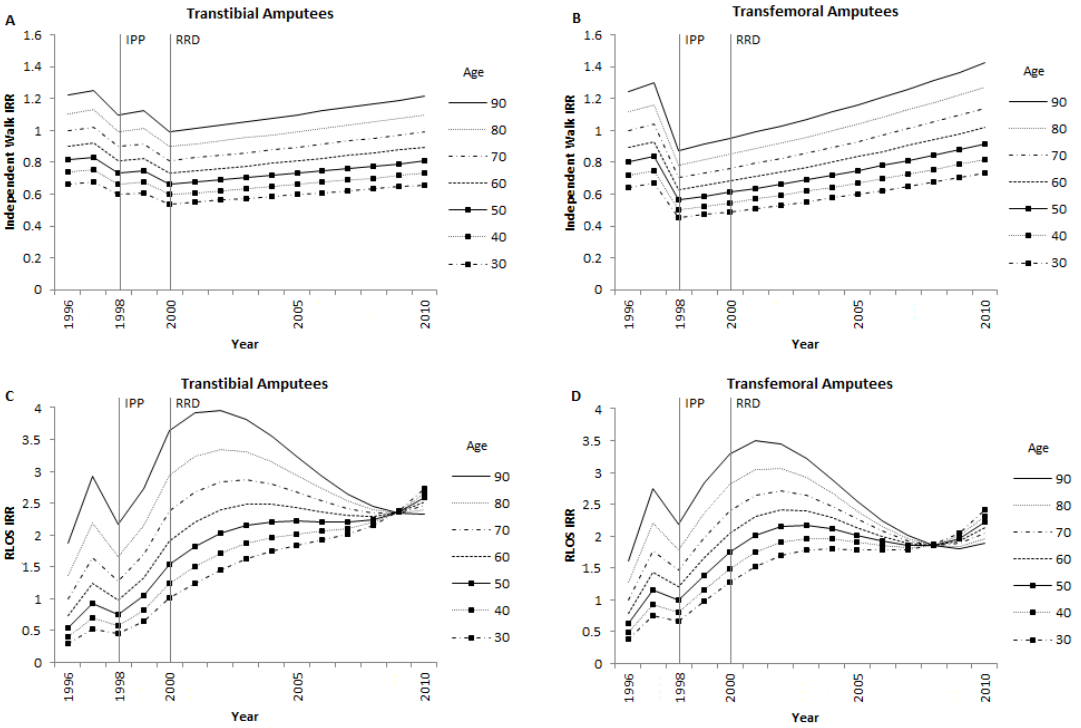

Figure 4.4: Change in IRR across the observation period for independent walk and inpatient rehabilitation LOS.

Time to independent walk for individuals with transtibial (A) and transfemoral (B) amputation, and inpatient rehabilitation LOS for individuals with transtibial (C) and transfemoral (D) amputation, based on age, with any indication for amputation, no comorbidities or complications.

4.5 Discussion

The aim of this study was to describe changes in the demographics and clinical characteristics of individuals with lower-limb amputation admitted to a Southern Adelaide area hospital for rehabilitation, and to determine how changes in these characteristics and service delivery over the period of observation have affected rehabilitation outcomes in the patient population. From these findings the broader significance to physiotherapists working with individuals with lower-limb

amputations are discussed.

Age, gender and indication for amputation of this cohort are similar to that reported by other recent Australian and international amputee rehabilitation cohorts (Aulivola et al. 2004; Cruz et al. 2003a; Kazmers, Perkins & Jacobs 2000; Lim et al. 2006; Nehler et al. 2003; Rommers et al. 1996; Toursarkissian et al. 2002; Wu, Chan & Bowring 2010). A higher percentage of transtibial amputees were admitted to the Repatriation General Hospital (68%) compared to previous published data (44%-59%), while a lower percentage of individuals with transfemoral amputation (22%) were seen compared to earlier data (26-55%) (Hubbard 1989; Jones, Hall & Schuld 1993; Katrak & Baggott 1980; Kazmers, Perkins & Jacobs 2000; Lim et al. 2006; Nehler et al. 2003). However, comparison with a more recent Australian cohort covering a similar observation period (1994-2006) reveals a similar percentage of transtibial amputees admitted for rehabilitation (66%) (Wu, Chan & Bowring 2010). The reported differences compared to historical published data are a reflection of the predominantly vascular nature of individuals with amputation admitted to the Repatriation General Hospital, advances and improvements in limb salvage surgery, diabetic care, foot care and wound management which have occurred in recent years.

Across the observation period there was a decrease in the number of individuals with lower-limb amputation discharged home despite the average age of patients decreasing significantly. One of the major reasons for this trend was the increasing number of comorbidities observed in this population which meant that overall patients were frailer and less appropriate for discharge home. One of the most common comorbidities in this population was type II diabetes mellitus. It is known

that the incidence of type II diabetes mellitus is increasing worldwide, primarily because of increasing prevalence of obesity and physical inactivity (Eckel, Grundy & Zimmet 2005; Hu 2011; Wild et al. 2004). Clinicians, including physiotherapists, may need to consider the implementation of chronic disease self-management approaches to promote changes leading to more healthy lifestyles amongst the amputee population (Heideman et al. 2011; Hu 2011; Tuomilehto et al. 2001).

Identifying improvements in the amputee rehabilitation service relied upon identifying important clinical outcomes and measuring them as changes were made to the service during the period of observation. Four primary outcomes were used in this study to monitor patient rehabilitation – wound healing, initial prosthetic casting, independent walk and inpatient rehabilitation LOS. Wound healing and time to first prosthetic casting are traditional milestones in amputee rehabilitation as early successful wound healing allows progression to further rehabilitation, including mobility with a prosthesis. The initial aim of clinicians, practitioners and medical staff is to promote wound healing since early successful wound healing is often immediately followed by prosthetic casting (Nawijn et al. 2005), as was demonstrated by the present data. Time from amputation to first prosthetic casting was similar to time frames reported in previous studies (Deutsch et al. 2005; Taylor et al. 2008). The initial casting for a prosthetic socket will lead to use of an interim prosthesis and a more intesive phase of rehabilitation with the ultimate goal being to achieve independent walking,

In contrast the time taken to achieve independent walking, which is a key rehabilitation goal for individuals with lower-limb amputation and amputee

physiotherapists, is not well reported in the literature. The ability to walk independently was achieved by a high percentage of patients (83%) in this study. This is well within the range (56%-97%) reported by Van Velzen et al., (Van Velzen et al. 2006). However, there was more variation in the time taken to achieve an independent walk in the current data due to changes in service delivery over the observation period. Reporting on time to independent walk should be included as a key measure in amputee rehabilitation studies to inform improvements in physiotherapy service delivery.

Interim prosthetic programs vary across rehabilitation sites. Only one previous study comparing a public and private IPP model could be found, but did not report on outcomes used in this study (Gordon et al. 2010). During the period of observation, the introduction of the IPP was associated with a significant reduction in the time taken to achieve initial prosthetic casting, independent walking and inpatient rehabilitation LOS, suggesting it is a valuable part of a service model. The reduction in time to initial prosthetic casting was not unexpected as the program supplied patients with an interim prosthesis which was not done previously. However, the reduction in time to independent walk has not been reported previously and is an important milestone for the patient in regaining independence (Hamamura et al. 2009; Pell et al. 1993). The reduction is primarily due to the IPP providing access to an interim prosthesis (figure 4.1), enabling individuals with lower-limb amputation to practice more appropriate patterns of weight shifting, stepping and walking with a physiotherapist sooner in the rehabilitation phase. Physiotherapists working with individuals with lower-limb amputations are encouraged to initiate service modifications, such as an IPP if one is not already in place, which facilitate mobility

retraining as soon as possible in the rehabilitation process.

The use of RRDs with individuals with transtibial amputation should now be common practice in many services across the developed world. The introduction of RRDs occurred in 2000 at the Repatriation General Hospital and was associated with a significant reduction in time from amputation to wound healing, initial prosthetic casting and independent walk for individuals with transtibial amputation. These findings are consistent with previous evidence which has demonstrated RRDs reduce time to wound healing (Deutsch et al. 2005; Nawijn et al. 2005), time to initial prosthetic casting (Hughes, Ni & Wilson 1998; Taylor et al. 2008; Woodburn et al. 2004; Wu, Keagy & Krick 1979) and rehabilitation LOS (Taylor et al. 2008). However, this study provides some of the first evidence to suggest that their use is associated with a reduction in the time taken to achieve independent walking. This is a key finding for physiotherapists as they are often primarily concerned with restoring the mobility of their patients. In consultation with treating physiotherapists and prosthetists, amputee rehabilitation services should ensure that individuals with transtibial amputation are provided with RRDs following limb amputation in accordance with best practice guidelines.

Despite the introduction of the IPP and RRDs it is interesting to note that times to initial prosthetic casting, independent walk and inpatient rehabilitation LOS based on IRRs are increasing towards the end of the observation period (see figure 4.3 and 4.4). These increases may be due to the earlier stage in acute recovery at which individuals with lower-limb amputation are admitted to rehabilitation from acute hospital services. Whilst this process may reduce acute hospital LOS, it may impact

negatively on rehabilitation LOS. However, this may be countered by the benefit of earlier exposure to physiotherapy rehabilitation services. These changes may also be due to the increase in a more comorbid population that is admitted for rehabilitation and indicate the need for an amputee rehabilitation service better tailored for this population. Further investigation is required into the increasing time to rehabilitation outcomes and how service provision can be improved to address these trends.

There are limitations of this study to acknowledge. This study was based at a single institution and there are likely to be differences in admission criteria and services provided to patients and therefore results may not be generalisable to other amputee rehabilitation facilities. Further limitations of this study include the retrospective nature of the analysis which relied upon the quality of documentation and recording in the physiotherapy clinical database and medical notes. Not all desirable data were available to undertake a complete and thorough analysis of the outcomes of the amputee rehabilitation service. For example, information regarding residual limb (stump) length, surgical technique, prosthetic equipment and premorbid mobility are all factors which were not documented in this study, but are likely to influence amputee rehabilitation outcomes. Finally, no follow-up of function in the community was conducted to determine the long term outcomes from the amputee rehabilitation.

4.6 Conclusion

Individuals with lower-limb amputation were typically elderly, vascular, males with transtibial amputations. Introduction of the IPP and RRDs successfully reduced time to all primary rehabilitation outcomes including, time to wound healing, initial

prosthetic casting, independent walk, and inpatient rehabilitation LOS. Three implications relevant for amputee physiotherapists and clinicians can be drawn from this study. Time to independent walk is an outcome of value which should be tracked by physiotherapists. For the present cohort it has proven a useful outcome in assessing the effectiveness of service modifications during the period of observation. Secondly physiotherapists need to consider service modifications which would enable individuals to undertake mobility retraining earlier in their rehabilitation to reduce time to rehabilitation milestones. Finally, in light of the changing characteristics of individuals with lower-limb amputation now presenting for rehabilitation described in this study it is likely physiotherapists, and clinicians in general, will need to tailor services to target this younger population with a higher number of comorbidities.

CHAPTER FIVE: ASSESSING GAIT VARIABILITY IN TRANSTIBIAL AMPUTEE FALLERS BASED ON SPATIAL-TEMPORAL GAIT PARAMETERS NORMALISED FOR WALKING SPEED

About this chapter:

The previous chapters have highlighted how amputees are now presenting with increasing comorbidities and this is associated with increased rehabilitation lengths of stay to achieve mobility. This chapter examined the characteristics of functional amputee gait in a group of forty-seven unilateral transtibial amputees using spatial-temporal gait analysis. In the literature review it was identified that a high proportion of amputees experience falls potentially due to altered biomechanics associated with prosthetic gait. Instrumented gait assessments can accurately quantify descriptors of gait function which may be associated with a propensity for falls, and thereby provide a clinically relevant marker which can be monitored. Spatial-temporal gait analysis is normally performed using repeated walk trials. This technique may result in gait speed variability, especially in populations where gait function is poor. Gait speed normalisation was investigated in the analysis of gait variability. Participants for this study were recruited from the rehabilitation facility described in chapter four, and 38% had peripheral vascular disease. This chapter addressed the research question ‘Is the variability of speed normalised spatial-temporal gait parameters an important gait biomarker associated with falls history in transtibial amputees?’ This chapter is currently under review at *Gait and Posture*.

5.1 Abstract

Variability in spatial-temporal features of gait has been associated with a history of falls in transtibial amputees. Commonly used protocols to assess gait employ multiple walking trials which may lead to increased intra-subject variability of walking speed, potentially confounding associated measures of spatial-temporal gait variability. The aim of this study was to determine if normalising spatial-temporal gait data for walking speed leads to differences in gait variability parameters associated with a history of falling in transtibial amputees. Forty-seven unilateral transtibial amputees were recruited, with forty-five completing the study (35 male, age 60.5 (SD13.7) years). Participants completed 10 consecutive walking trials over an instrumented walkway. Primary outcomes measures were step-length, step-width, swing-time and step-time variability. Participants provided a retrospective 12-month falls history. Sixteen (36%) amputees were classified as fallers. Variation in gait speed across the 10 walking trials was 2.9% (range 1.1% - 12.1%). Variability parameters of normalised gait data were significantly different to variability parameters of non-normalised data (all $p < 0.01$). For non-normalised data, fallers had greater amputated limb step-time ($p = 0.02$), step-length ($p = 0.02$), swing-time ($p = 0.05$), step-width ($p = 0.03$) variability and non-amputated limb step-length ($p = 0.04$) and step-width ($p = 0.01$) variability. For normalised data only three variability parameters remained significantly greater for fallers. These were amputated limb step-time ($p = 0.05$), step-length ($p = 0.02$), and step-width ($p = 0.01$) variability. Normalising spatial-temporal gait data for walking speed before calculating gait variability parameters may lead to improved specificity of the variability parameters related to falls history in transtibial amputees. It is recommended a similar

normalisation procedure be adopted for protocols using multiple walking trials to assess gait variability.

5.2 Introduction

Variability in spatial-temporal features of gait has gained increased attention as a potential biomarker to characterise disturbances in the regulation of gait. Higher levels of gait variability are associated with an increased falls risk for transtibial amputees (Parker, Hanada & Adderson 2013; Vanicek et al. 2009). Sensitive measures of falls risk are essential for clinicians involved in lower-limb amputee rehabilitation given the high incidence of falls (Miller, Speechley & Deathe 2001). However, appropriate procedures to assess gait variability are still a subject of debate (König et al. 2014).

A key issue in employing protocols to examine gait variability is whether normalising for walking speed is necessary as differences in walking speed can affect the relative duration of phases of the gait cycle and magnitude of spatial-temporal gait parameters (Beauchet et al. 2009). Most protocols record multiple individual over-ground walking trials using instrumented walkways (Lord et al. 2011b) or motion capture systems (Vanicek et al. 2009). The stop-start nature of the walking trials likely increases intra-subject variability of walking speed, particularly for patients with existing gait deficits such as transtibial amputees. Accordingly intra-subject speed variability should be accounted for prior to calculating variability measures. Previous studies have attempted to control intra-subject variability of walking speed through use of paced walking or treadmills (Krebs et al. 2002), however this risks imposing an atypical gait pattern. Controlling statistically for mean walking speed across trials has limitations and may remove important gait parameters relevant to aspects of pathology (Astephen Wilson 2012).

Normalising gait parameters is common when describing the mechanics of gait. This may include time normalising the duration of the gait cycle as a percentage or normalising spatial gait parameters by an individual's height or leg length. While previous studies have attempted to normalise for walking speed (Helbostad & Moe-Nilssen 2003; Van Iersel, Olde Rikkert & Borm 2007), none have investigated whether this affects the variability parameters associated with a history of falling. Understanding this relationship may have important clinical implications for determining falls risk. The aim of this study was to determine if normalising spatial-temporal gait data for walking speed leads to differences in gait variability parameters associated with falls histories in transtibial amputees. It was hypothesised not all variability parameters associated with a falls history would remain significant after normalising for walking speed.

5.3 Methods

5.3.1 Participants

Forty-seven amputees were recruited to participate in this study. Two were excluded due to inability to recall falls history. Forty-five unilateral transtibial amputees (35 male, age 60.5 (SD 13.7) years, 15.9 (SD 19.1) years since amputation) with well-fitting prostheses completed the study. Primary amputation pathologies were peripheral vascular disease (38%) and trauma (38%). Demographics and clinical characteristics of participants are provided in table 5.1. Ethical approval was provided by the Southern Adelaide Clinical Human Research ethics committee and

all participants provided written informed consent in accordance with the Declaration of Helsinki.

Table 5.1: Demographics and clinical characteristics of participants.

Demographics and Clinical Characteristics	Faller (n = 16)	Non-Faller (n = 29)	Total (n =45)
Age (years, mean (SD))	64.4 (13.5)	58.5 (13.3)	60.5 (13.7)
Gender (n (%) male)	10 (63%)	25 (86%)	35 (78%)
Indication for amputation, n(%)			
PVD	9 (56%)	8 (31%)	17 (38%)
Trauma	6 (38%)	11 (28%)	17 (38%)
Other	1 (6%)	10 (26%)	11 (24%)
Stump-length (cm, mean (SD))	17.7 (2.6)	16.7 (3.4)	17.0 (3.1)
Time since amputation (years, mean (SD))	13.2 (19.1)	18.0 (19.2)	15.9 (19.1)

PVD, peripheral vascular disease. Other indications for amputation include congenital, infection and tumor.

5.3.2 Procedures

Gait was assessed with an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA) which captured individual footfall data over an area 4.9m x 0.6m, sampled at 120Hz. Participants completed 10 consecutive walking trials at their self-

selected comfortable walking speed starting and stopping two metres from the ends of the walkway. Step parameters were selected in preference to stride parameters for improved clinometric properties (Moe-Nilssen et al. 2010). Primary outcome measures were step-length, step-width, swing-time, and step-time variability due to previous use with amputees and older adults (Brach et al. 2008; Parker, Hanada & Adderson 2013; Vanicek et al. 2009). To determine the effect of intra-subject variability of walking speed on gait variability, spatial-temporal gait data of each walking trial were normalised by dividing by the walking speed of the respective trial. The formula for calculating speed normalised variability measures was; normalised spatial-temporal gait parameter = (spatial-temporal gait parameter/walk speed). This calculation was performed for individual trials (10 trials in total) for each participant. Mean variability (coefficient of variation, CV) parameters were then calculated for the 10 walking trials.

The purpose of this methodology is to account for variations in stepping pattern that contribute to changes in walk speed between individual trials. Therefore, the variability measures reported are more likely to reflect motor control of the stepping pattern. For example, an amputee who increases or decreases walk speed between individual trials by making small adjustments in step-length would likely be identified as having greater step-length variability. However, this would not necessarily reflect motor control of the lower-limb, which is generally considered the purpose of assessing gait variability (Hausdorff 2007). Instead, the methodology used in this study accounts for the effects of changes in walk speed between trials and therefore the normalised step-length variability would be less than the non-

normalised step-length variability, and is more likely to reflect motor control of the limbs.

Participants were classified as a non-faller (no falls in past 12 months) or faller (one or more falls in past 12 months) based on an interview which obtained a retrospective falls history. A fall was defined as ‘an event which caused the participant to unintentionally end up on the ground or lower surface (Askham et al. 1990).

5.3.3 Analysis

Normality of data were checked and where assumptions were not met, non-parametric statistics were applied. Separate independent t-tests analysed age and stump-length for falls history. Separate chi-square analyses tested reason for amputation and gender for falls history. Intra-subject speed variability and time since amputation were analysed for falls history with a Mann-Whitney U-test. Individual Wilcoxon Signed-Rank Tests analysed differences between individual non-normalised and normalised gait variability parameters. Mann-Whitney U-tests were used to analyse both non-normalised and normalised gait variability parameters for falls history. Significance level was set at $p \leq 0.05$ and SPSS software was used for analyses (IBM corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0).

5.4 Results

Sixteen (36%) amputees were classified as fallers. No differences existed between groups for gender ($p = 0.07$), reason for amputation ($p = 0.09$), age ($p = 0.16$), stump-length ($p = 0.33$) or time since amputation ($p = 0.22$). Median intra-subject speed variability was 2.9% (range 1.1% - 12.1%), and was greater in fallers (median 3.6%, IQR 2.5 - 5.2) than non-fallers (median 2.8%, IQR 2.3 - 3.7), although this did not reach significance ($p = 0.09$). All normalised gait variability parameters were significantly different to non-normalised variability parameters (see table 5.2).

Table 5.2: Median (IQR) non-normalised and normalised spatial-temporal gait variability parameters

	Non-Normalised Gait Variability	Normalised Gait Variability	Statistic
Step-length AL (%)	4.2 (2.8-5.3)	2.6 (1.7-3.4)	$p < 0.001$
Step-length NAL (%)	4.4 (2.9-6.1)	2.4 (1.8-3.6)	$p < 0.001$
Step-width AL (%)	15.9 (11.4-20.9)	11.8 (8.5-15.7)	$p < 0.001$
Step-width NAL (%)	15.9 (12.1-21.4)	11.6 (8.2-15. 1)	$p < 0.001$
Step-time AL (%)	3.2 (2.4-4.1)	4.4 (3.4-7.2)	$p < 0.001$
Step-time NAL (%)	3.4 (2.5-4.3)	4.7 (3.8-6.7)	$p < 0.001$
Swing-time AL (%)	3.5 (2.8-5.1)	4.5 (3.6-6.3)	$p < 0.001$
Swing-time NAL (%)	4.2 (3.1-5.4)	4.6 (3.9-6.5)	$p = 0.009$

AL, amputated limb

NAL, non-amputated limb

5.4.1 Non-normalised spatial-temporal gait variability

For non-normalised parameters, fallers had greater amputated limb step-length ($U_{(43)}$ = 135.0, p = 0.02), step-width ($U_{(43)}$ = 151.0, p = 0.03), step-time ($U_{(43)}$ = 136.0, p = 0.02), and swing-time variability ($U_{(43)}$ = 154.5, p = 0.05). On the non-amputated limb, fallers had greater step-length ($U_{(43)}$ = 144.0, p = 0.04) and step-width variability ($U_{(43)}$ = 138.0, p = 0.01). No other parameters reached significance (see table 5.3).

5.4.2 Normalised spatial-temporal gait variability

For normalised parameters, fallers had greater amputated limb step-length ($U_{(43)}$ = 134.0, p = 0.02), step-width ($U_{(43)}$ = 138.0, p = 0.01), and step-time variability ($U_{(43)}$ = 149.0, p = 0.05). No other parameters reached significance (see table 5.3).

Table 5.3: Median (IQR) non-normalised and normalised spatial-temporal gait variability parameters for fallers and non-fallers

	Non-Normalised Gait Variability		Normalised Gait Variability	
	Faller (N = 16)	Non-Faller (N = 29)	Faller (N = 16)	Non-Faller (N = 29)
Step-length AL (%)	**4.8 (4.1-6.6)**	**3.8 (2.6-4.8)**	**3.2 (2.3-4.0)**	**2.2 (1.7-3.0)**
Step-length NAL (%)	**5.4 (3.6-7.3)**	**3.7 (2.4-5.5)**	2.9 (2.0-3.8)	2.1 (1.6-3.0)
Step-width AL (%)	**16.9 (11.5-24.9)**	**12.5 (9.9-17.2)**	**13.1 (10.9-16.2)**	**10.2 (7.6-12.0)**
Step-width NAL (%)	**16.3 (13.8-24.7)**	**13.6 (10.4-17.1)**	12.7 (8.9-18.4)	11.4 (7.5-14.1)
Step-time AL (%)	**3.7 (3.2-4.6)**	**2.8 (2.2-3.8)**	**4.9 (4.1-7.9)**	**4.0 (3.1-6.1)**
Step-time NAL (%)	3.8 (2.7-6.0)	3.3 (2.4-4.0)	5.0 (4.3-7.8)	4.5 (3.6-5.8)
Swing-time AL (%)	**3.9 (3.0-6.3)**	**3.4 (2.6-4.5)**	5.6 (4.0-7.1)	4.1 (3.3-6.1)
Swing-time NAL (%)	4.0 (3.4-6.1)	4.2 (2.8-5.4)	4.8 (3.9-6.9)	4.3 (3.8-5.9)

Bold text indicates significant differences between fallers and non-fallers.

AL, amputated limb

NAL, non-amputated limb

5.5 Discussion

It is reasonable to expect natural variations in walking speed will be increased for protocols using multiple over-ground walking trials to assess spatial-temporal gait variability due to the stop-start nature of the walking trials. In this study transtibial amputees showed up to 12% intra-subject speed variability which is greater than that of age and gender matched healthy adults from our laboratory (range 1.6-5.2%, unpublished data). Normalising spatial-temporal gait data for walking speed will help minimise any confounding speed dependent effects which may otherwise be reflected in the magnitude of associated gait variability measures. This study showed that the magnitude of gait variability parameters from speed normalised spatial-temporal gait data were significantly different to variability parameters of non-normalised data. This finding supports previous work indicating that normalising for walking speed is an important consideration when assessing gait variability (Beauchet et al. 2009; Helbostad & Moe-Nilssen 2003; Kang & Dingwell 2008). Moreover, normalising spatial-temporal gait parameters for walking speed revealed improved specificity in gait variability parameters associated with histories of falling in this group of transtibial amputees. The clinical significance of this finding remains to be determined, but it is interesting to note that when normalising for walking speed, greater spatial-temporal variability in the stepping pattern of the amputated limb during gait distinguished fallers from non-fallers, while associated variability of the non-amputated limb did not discriminate between the groups.

5.6 Conclusion

While there are limitations to the present cross sectional study, namely the use of a small opportunity sample and retrospective falls histories, the present data suggests that in transtibial amputees increased intra-subject variability in walking speed assessed over multiple walking trials may lead to some spatial-temporal gait variability parameters being incorrectly associated with histories of falling. It is therefore recommended future studies employing similar protocols normalise spatial-temporal gait data from individual walking trials for walking speed before calculating associated variability parameters, otherwise there may be an increased chance of false positives when characterising the association of gait variability parameters with histories of falling. This may be particularly relevant for clinical populations where variability in walking speed may be greater due to existing musculoskeletal or neurological impairments (Waters & Mulroy 1999).

CHAPTER SIX: USE OF AN ACTIVITY MONITOR AND GPS DEVICE TO ASSESS COMMUNITY ACTIVITY AND PARTICIPATION IN TRANSTIBIAL AMPUTEES

About this chapter:

In the previous chapter it was identified that normalised gait variability is a sensitive measure of gait function that can be assessed clinically. This chapter sought to investigate the relationship between gait variability and measures of community integration. Presence of this relationship would further signify importance of assessing gait variability in the clinic. For the purpose of this study wearable technology was utilised as a novel method to assess community activity and participation. Participants recruited for this study were the same cohort of participants studied in chapter five. This chapter addressed the research question 'Can wearable technology be used to assess community mobility function in transtibial amputees, and are measures of community mobility function associated with clinical assessments of normalised gait variability and falls history?'. Results of this study have been published in *Sensors*.

6.1 Abstract

This study characterised measures of community activity and participation of transtibial amputees based on combined data from separate accelerometer and GPS devices. Forty-seven participants were recruited (79% male, mean age 59.7 years). Participants wore the accelerometer and GPS devices for seven consecutive days. Data were linked to assess community activity (community based step counts) and community participation (number of community visits) per day. Community activity and participation were compared across amputee K level groups. The relationships between community activity and participation measures and clinically assessed gait variability and falls history were investigated. On average each participant completed 2,378 (SD 1,896) community steps per day and 2.3 (SD 1.6) community visits per day over a seven day period. There were differences between K level groups for measures of community activity ($p < 0.001$) and participation ($p = 0.002$) with lower functioning K1/2 amputees demonstrating lower levels of community activity and participation than K3 and K4 amputees. There was no significant difference between K3 and K4 for community activity ($p = 0.28$) or participation ($p = 0.43$). Significant negative relationships were identified between measures of community activity and participation and gait variability. Participants with falls history demonstrated significantly lower levels of community activity ($p = 0.01$) and participation ($p = 0.04$). Specifically, activity levels were reduced for recreational ($p = 0.05$) and commercial roles ($p = 0.04$), while participation was lower for recreational roles ($p = 0.04$). This study demonstrated methodology to link accelerometer and GPS data to assess community activity and participation in a group of transtibial amputees. These findings highlight the potential of wearable technology to assist understanding of

activity and function in rehabilitation and further emphasises the importance of clinical gait and falls assessments to improve overall quality of life in this population.

6.2 Introduction

Successful reintegration into the community following lower-limb amputation is a key aim of both rehabilitation clinicians and patients (Corrigan & McBurney 2008; Esquenazi & DiGiacomo 2001; Goldberg 2006; Hill et al. 1997). Community integration may be characterised by the domains of activity and participation as outlined in the International Classification of Functioning, Disability and Health (WHO 2001). Prosthetic mobility is an activity which has been associated with improved quality of life (Pell et al. 1993), greater involvement in social activities (Gerhards, Florin & Knapp 1984; Pell et al. 1993) and activities of daily living (Collin, Wade & Cochrane 1992; Datta, Nair & Payne 1992), and is important for participation in employment and recreational roles (Brown et al. 2009). Following amputation only 26%–62% of patients achieve outdoor mobility (Van Velzen et al. 2006) limiting the capacity to participate in the community. For clinicians and researchers, assessment of community activity and participation following rehabilitation is a key marker of successful prosthetic rehabilitation and intervention effectiveness. Therefore there is a need to accurately quantify these domains.

Typically, the domains of activity and participation are assessed using either subjective or objective measures. Subjective measures, such as the Locomotor Capabilities Index (Grise, Gauthier-Gagnon & Martineau 1993) and activity diaries, have been shown to be unreliable and overestimate activity in lower-limb amputees (Smith, Brown & Ubel 2008; Stepien et al. 2007). Conversely, performance on objective clinical assessments have shown moderate to strong correlations with community based activity measures (Parker et al. 2010), and may be representative

of the capacity to perform that activity in the community. Objective measures of ambulatory function are used by clinicians to guide prosthetic prescription and assess outcomes from rehabilitation. However, a limitation of clinical assessments is that they fail to replicate the range of physical demands and unpredictable nature of community ambulation and participation, and as such, these measures may not accurately reflect actual levels of community activity and participation (Corrigan & McBurney 2008). A commonly used objective measure of amputees function is the AMP-PRO (Gailey et al. 2002). Briefly, the AMP-PRO assesses a range of functional activities providing a score which assists in classifying amputee K levels (K0, K1, K2, K3, K4) and guiding prosthetic prescription (Health Care Financing Administration 2001). Higher K levels (e.g., K4) indicate amputees with potential for greater functional ability, who may benefit from more advanced prosthetic componentry (Gailey et al. 2002).

With recent advances in wearable technology (Patel et al. 2012), accelerometer-based monitoring devices to assess step-counts and GPS devices to assess location offer the ability to obtain accurate objective measures of community activity and participation (Bonato 2005; Bonato 2009; Kang et al. 2013; Patel et al. 2012; Rodriguez et al. 2012; Troped et al. 2008). Activity data derived from accelerometer devices has been successfully collected in amputees previously (Klute et al. 2006; Parker et al. 2010; Stepien et al. 2007), but, by its nature, does not provide information about the location in the community where the activity occurs. The addition of GPS data provides a means of mapping position in the community, but introduces challenges for ensuring reliable data capture and synchronisation with activity data (Kerr, Duncan & Schipperjin 2011). Recently, GPS and step count data

were collected in a transfemoral amputee case study, demonstrating potential to provide accurate information for clinicians (Jayaraman et al. 2014). However, it is currently unknown if separate accelerometer and GPS data can be captured simultaneously and successfully linked in order to assess community activity and participation in a larger cohort of transtibial amputees. Additionally, studies which have used separate wearable technology devices to determine if differences do exist for community activity and participation between amputee K levels were unable to be identified. It is important for the field of amputee rehabilitation to further investigate the use of wearable technology to assess community activity and participation, and determine the nature of relationships between community and clinic based measures.

Spatial-temporal gait variability is a clinically assessed measure which may be associated with community activity and participation. Identifying appropriate clinical measures associated with community integration is important for rehabilitation clinicians. Gait variability assessments are often used to identify falls risk (Hausdorff, Rios & Edelberg 2001; Montero-Odasso et al. 2011; Parker, Hanada & Adderson 2013; Paterson, Hill & Lythgo 2011; Vanicek et al. 2009; Verghese et al. 2009). However, there is also suggestion that fluctuations in spatial-temporal gait parameters (step-time and step-length) are associated with decreased walking confidence, fear of falling, a reduction in daily physical activities and social function (Hausdorff, Rios & Edelberg 2001; Reelick et al. 2009), although this is yet to be investigated in lower-limb amputees. Similarly, falls history has been linked to reduced functional mobility, decline in independence and self-imposed restriction of community activity for older adults (Howland et al. 1998; Tinetti et al. 1994b; Vellas

et al. 1997). Given the high frequency of falls, and fear of falling experienced by some amputees (Miller et al. 2001; Miller, Speechley & Deathe 2001), it is plausible that participation in the community may be affected. Identifying potential relationships with community activity and participation in lower-limb amputees would highlight importance of clinical gait and falls assessments, and further demonstrate importance of wearable technology as an objective assessment of community integration.

The primary aim of this study was to assess the ability to use wearable technology (accelerometer-based monitor and GPS devices) to measure community activity and participation in rehabilitated transtibial amputees. Measures of community activity and participation will be compared between amputee K levels. The secondary aim was to determine if relationships exist between levels of community activity and participation and clinical measures of gait variability identified in chapter five of this thesis. A further analysis was conducted to determine if community activity and participation differed between amputees based on falls history. It was hypothesised that the combination of accelerometer and GPS data to assess community activity and participation would be feasible. In addition, a negative relationship between gait variability and community activity and participation would be observed, and amputees with a history of falls would have lower levels of community activity and participation.

6.3 Methods

6.3.1 Participants

Forty seven rehabilitated unilateral transtibial amputees were recruited. All participants had been correctly fitted with a definitive prosthesis at least six months prior to testing, and correct prosthetic fit and comfort were confirmed with the participant and their prosthetist prior to inclusion in the study. Participants were eligible if they achieved prosthetic mobility. Amputees not provided with a prosthesis for mobility (functional level K0) were excluded. The majority of recruited participants were male (79%), with a mean age of 59.7 (range 19–98) years. Primary indications for amputation were trauma (38%) or peripheral vascular disease (38%). Ethical approval was provided by the Southern Adelaide Clinical Human Research ethics committee and all participants provided written informed consent in accordance with the Declaration of Helsinki.

6.3.2 Equipment

6.3.2.1 Step activity monitor

A StepWatch3 Activity Monitor (SAM) (Cyma Corp, Seattle, WA, USA) was fitted to each participant's prosthesis in accordance with manufacturer's recommendations. The SAM is an accelerometer and microprocessor based activity monitor measuring 6.5 cm × 5.0 cm × 1.5 cm verified for use in people with lower-limb amputations (Coleman et al. 1999). The SAM was set to record stride count data for each minute of programmed use (Parker et al. 2010). Step count data were obtained by multiplying the stride count by two. Data from the SAM were downloaded using StepWatch software (version 3.1b), and stored within the software database.

6.3.2.2 Global positioning system

A QStarz BT-Q1000XT (Qstarz International Co., Ltd., Taipei, Taiwan) 66-channel tracking GPS travel recorder was used to record latitude, longitude, local date and time of each participant's position for every five seconds of programmed use. The device measures 7.2 cm × 4.7 cm × 2.0 cm, has a battery life of 42 h and accuracy error of less than three metres. Data from the GPS unit were imported to QTravel software (version 1.46) and stored within the software database.

6.3.3 Procedure

Participants were supplied with SAM and GPS devices. Both devices were secured to the participant's prosthesis with a single Velcro strap (see figure 6.1). The devices remained attached to the prosthesis for the duration of the study period. The SAM and GPS devices were programmed for data collection using separate networked computers, thereby ensuring local time for each device was identical and preventing mismatched times in the data linkage process. Participants wore the SAM and GPS devices for a period of seven consecutive days and were supplied with a battery charger and clear written instructions for charging the GPS device nightly (Evenson et al. 2013). At the time of provision of SAM and GPS devices, clinical characteristics (age, time since amputation and indication for amputation), employment status and standard clinical measures were collected. These standard clinical measures were the AMP-PRO and functional gait analysis. Gait analysis was performed using an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA) with embedded pressure sensors to capture individual footfall data over an active area of 4.9 m × 0.6 m. Participants completed 10 consecutive walking trials over the GAITRite at their self-selected gait speed. Data were collected at 120 Hz

and analysed using GAITRite software (version 4.5.5). For each trial spatial-temporal parameters were normalised for walking speed using methodology identical to that reported in chapter five. Variability of spatial-temporal parameters were reported as CV. The three spatial-temporal gait variability measures of interest were step-time, step-length, and step-width of the amputated limb. The significance of these measures has previously been identified in chapter five. Retrospective 12-month falls history was determined with an interview. Falls were defined as ‘an event which caused the participant to unintentionally end up on the ground or lower surface’ (Askham et al. 1990). Participants were classified as a faller (one or more falls in past 12 months) or non-faller (no falls in past 12 months).

Figure 6.1: The SAM and GPS devices attached to a prosthesis for data collection.

The SAM was positioned according to the manufacturer's recommendations. The GPS was attached to the same strap as the SAM device for convenience.

6.3.4 Data analysis

6.3.4.1 Data linkage

Datasets obtained from the SAM and GPS devices were exported as comma-separated value files from the respective software for each device. Within Microsoft Excel (2010) both SAM and GPS datasets were ordered chronologically and trimmed to ensure each dataset contained only seven consecutive complete periods of 24 h. As the SAM data were recorded per minute and the GPS per five seconds, local time of recorded data for both the SAM and GPS were trimmed to hour and minute values only so that the two sets of time values were identical. Local time for each dataset was converted to a time value ranging from 0 to 0.99930556, representing unique time values from 00:00 to 23:59. In a similar manner local date was converted to a date value represented as an integer for dates ranging from 1 January 1900 to 31 December 9999. A variable coded as Time_Date was generated in both datasets as a unique local time and date identifier and was calculated as the addition of the time value and date value. Latitude and longitude data obtained from the GPS were linked to step count data using Microsoft Excel's "lookup" function to link the unique Time_Date variable created. Similar use of date and time stamps has been reported in previous studies to link data from various forms of wearable technology (Hurvitz et al. 2014; Rodríguez et al. 2012). As a result of reducing GPS local time data to hour and minute values, up to 12 GPS latitude and longitude values were available for each minute of recorded data, and in this instance, the first latitude and longitude data values were used to link to the SAM dataset. The final linked dataset therefore contained step count and GPS latitude and longitude data for each minute of the seven consecutive days of data collection. Community visits were defined as events

where the participant left their home and attended a location in the community (WHO 2001). Individual community visits were analysed by recounting latitude and longitude data for the assessed seven consecutive day period in chronological order within QTravel (version 1.46). QTravel incorporates Google Maps and Google Earth software which utilises satellite imagery to provide geographic information. Community visit events were visually identified from this geographic information. These events were then manually coded as one of seven community participation categories external to the participants home (see figure 6.2 for a description of categories). If required verbal confirmation was obtained from participants ensuring accurate identification of community participation. Community participation, defined as involvement in life situations (WHO 2001), was assessed as the total number of individual visits to these categories. Community activity was assessed as the total step count out of home and was calculated as the sum of step counts across the seven community participation categories (Lord et al. 2004; WHO 2001).

Community Participation Categories

Category	Examples
Employment	Paid employment activities
Residential	Housing other than own home
Commercial	Shopping centres, local shops
Health services	Hospital, general practitioner, physiotherapist, chiropractor, pharmacist
Recreational	Oval, sports, beach, walk in community
Social	Restaurant, café, hotel, cinema
Other	Petrol station, council chambers

Figure 6.2: The seven community categories with examples which were used to assess community activity and participation in rehabilitated transtibial amputees.

6.3.4.2 Statistical analysis

The normality of data were checked with a Shapiro-Wilk normality test and where assumptions for parametric tests were not met, non-parametric statistics were used. To assess completeness and quality of GPS data missing GPS data points (%) prior to linkage, and missing step count data (%) in the linked dataset were assessed. Missing GPS data were assessed by comparing the expected number of cells with recorded data (n = 120,960) to observed number of cells with recorded data. Missing step count data from the linked datasets were analysed as the difference between step counts linked to GPS data and total step counts from the SAM. Descriptive statistics were used to characterise community activity based step counts and community

participation visit data for each of the community participation categories. Amputee K levels were analysed as three separate groups due to the low number of recruited amputees in the K1 and K2 categories. The categories were K1/2, K3, and K4. Clinical characteristics of age and time since amputation were analysed between K level groups using separate one-way ANOVAs. Employment status and indication for amputation (peripheral vascular disease, trauma, other) were analysed between K level groups with a Chi-Square test. Separate one-way ANOVAs were used to determine if there were differences in community based step counts and community visits. Post-hoc analyses were performed for ANOVA analyses with significant results using Bonferroni adjustment. Association between clinically assessed gait variability and measures of activity and participation were examined with Spearman rho tests. Potential contributions to differences in activity and participation between fallers and non-fallers were investigated. Differences in age for fall history were investigated with an independent t-tests. Differences in time since amputation and AMP-PRO scores for fall history were investigated with separate Mann-Whitney U tests. Differences in gender, indication for amputation, K-levels and employment status for fall history were investigated with separate chi-square analyses. Activity and participation were compared between amputees with history of falls and those with no falls history with separate independent t-tests overall, and for each community category. Significance level was set at $p \leq 0.05$ and SPSS software was used for all statistical analyses (IBM corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0).

6.4 Results

A total of 47 transtibial amputees were recruited to participate in the study. One was excluded due incomplete GPS data resulting from failure to charge the GPS battery as instructed. For the remaining 46 datasets, 6.5% (SD 7.3%) of GPS data were unavailable due to lost signal. As a result of incomplete GPS data due to signal loss, 5.3% (SD 5.9%) of all steps recorded by the SAM were not linked to GPS positional data. Fifteen amputees (33%) were employed during the period of data collection. For the measures of community activity and participation, amputees completed on average 2,378 (SD 1,896) steps in the community per day, and visited 2.3 (SD 1.6) community facilities per day over a consecutive seven day period. A summary of activity and participation measures is provided in table 6.1.

Table 6.1: A summary of community activity and participation for each participation category.

Activity	Step Count Mean (SD) per day	Community Visit Mean (SD) per day
Employment	2,332 (2,307)	1.5 (1.7)
Residential	371 (452)	0.4 (0.4)
Commercial	558 (586)	0.7 (0.5)
Health Service	111 (183)	0.2 (0.2)
Recreational	279 (515)	0.1 (0.2)
Social	248 (502)	0.3 (0.2)
Other	350 (723)	0.1 (0.2)
Total for Community Categories	2,378 (1,896)	2.3 (1.6)
Home	516 (293)	-
Lost in linkage	336 (440)	-
Unidentified	32 (87)	-

Lost in linkage = step count data that were recorded on the SAM while there was inadequate satellite signal for the GPS device; Unidentified = step count data that were unable to be categorised as one of the seven community participation categories, or home. Employment data representative of amputees who were employed (n = 15). All other community categories representative of all amputees (n = 46).

Clinical characteristics (age, time since amputation and indication for amputation) and employment status were analysed for K level categories. There were significant differences between K level categories for age ($F_{(2,43)} = 4.2$, $p = 0.02$). Post-hoc analysis revealed K1/2 amputees were older than K4 amputees (95%CI 4.8–29.9, $p = 0.01$). There was no significant difference in age between K1/2 and K3 amputees ($p = 0.10$), or between K3 and K4 amputees ($p = 0.17$). There was no significant difference for time since amputation ($p = 0.10$), indication for amputation ($p = 0.13$) or employment status ($p = 0.08$) (see table 6.2).

Table 6.2: Clinical characteristics for K level categories.

	K1/2 (*n* = 5)	**K3 (*n* = 13)**	**K4 (*n* = 28)**	**Statistic**
Age (years), mean (SD)	74.2 (14.8)	62.9 (16.8)	57.1 (9.8)	$p = 0.02$
Time since amputation (years), mean (SD)	5.8 (8.5)	9.7 (13.9)	20.7 (21.2)	$p = 0.10$
Indication for amputation, n (%)				$p = 0.13$
PVD	4 (8.7%)	7 (15.2%)	7 (15.2%)	
Trauma	1 (2.2%)	4 (8.7%)	14 (30.4%)	
Other	0 (0%)	2 (4.3%)	7 (15.2%)	
Employed, n (%)	0 (0%)	3 (23%)	13 (46%)	$p = 0.08$

PVD, peripheral vascular disease; other indications for amputation include congenital, infection and tumour.

There were differences between K level groups for the defined measures of community activity ($F_{(2,43)} = 9.4$, $p < 0.01$) and community participation ($F_{(2,43)} = 6.9$, $p = 0.01$). As expected, post-hoc analysis revealed K1/2 amputees completed significantly less community steps than K3 amputees (95%CI: 8.2–128.3, $p = 0.02$) and K4 amputees (95%CI: 39.2–150.0, $p < 0.01$). However, there was no significant difference in the number of community steps between K3 amputees and K4 amputees ($p = 0.28$). For community participation, post-hoc analysis revealed K1/2 amputees were involved in significantly less community visits than K3 amputees (95%CI: 0.01–0.64, $p = 0.05$) and K4 amputees (95%CI: 0.14–0.74, $p < 0.01$). However, there was no significant difference in the number of community visits undertaken by K3 and K4 amputees ($p = 0.43$). Community activity and participation for K level groups are summarised in table 6.3.

Table 6.3: Mean (SD) community measures per day for K level categories.

	K1/2 (*n* = 5)	**K3 (*n* = 13)**	**K4 (*n* = 28)**
Community Step Count	197 (145)	2,069 (2,369)	2,780 (1,574)
Community Visit	1.0 (0.6)	2.0 (0.8)	2.8 (1.8)

For all participants, median (IQR) normalised step-length variability was 2.6% (1.7% - 3.4%), step-time variability was 4.4% (3.4% - 7.2%), and step-width variability was 11.8% (8.5% - 15.7%). There was a significant negative relationship between community activity (community step-count) and step-length variability ($r_s = -0.29$, $p = 0.03$) (figure 6.3), but not step-time variability or step-width variability (all $p > 0.22$). There were significant negative relationships between community

participation (community visits) and step-length variability (r_s = -0.31, p = 0.02) (figure 6.4) and step-time variability (r_s = -0.26, p = 0.04) (figure 6.5) but not step-width variability (p > 0.09).

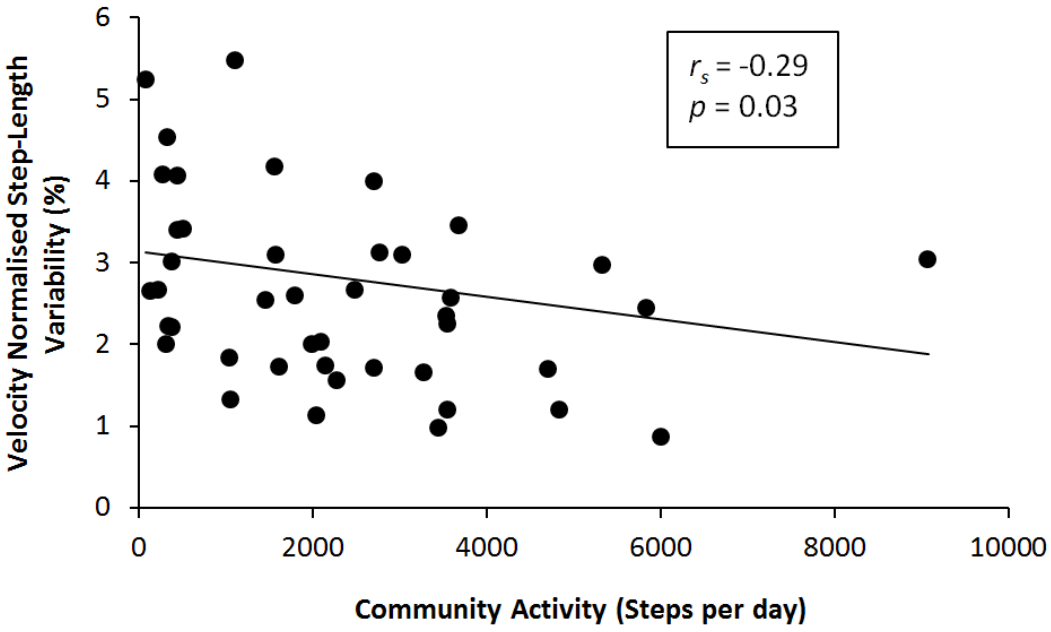

Figure 6.3: The association between clinically assessed step-length variability and community activity. Greater normalised step-length variability was associated with reduced community activity.

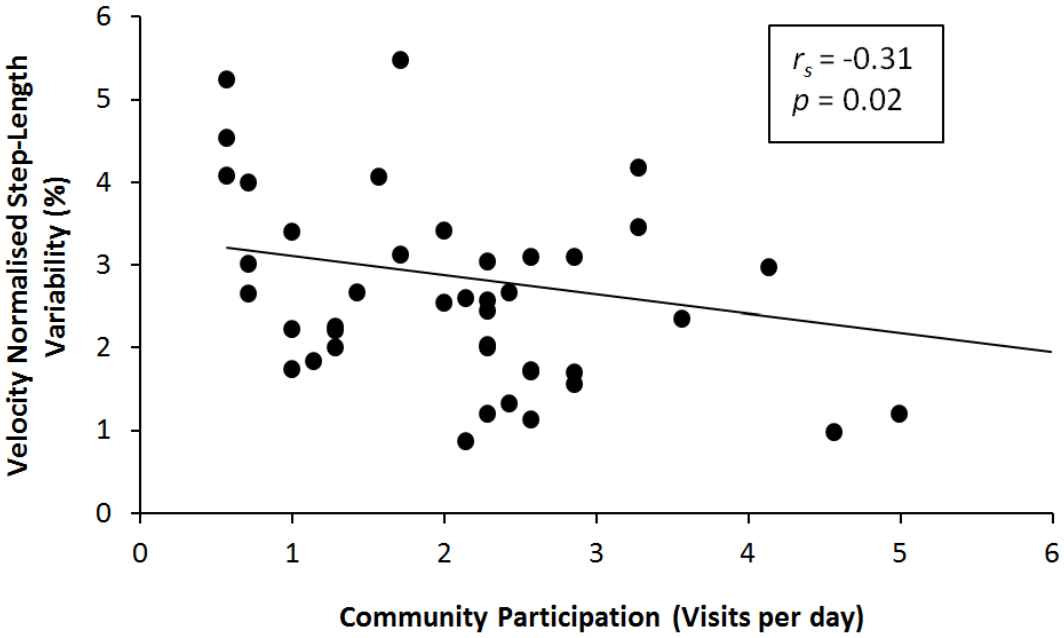

Figure 6.4: The association between clinically assessed step-length variability and community participation. Greater normalised step-length variability was associated with reduced community participation.

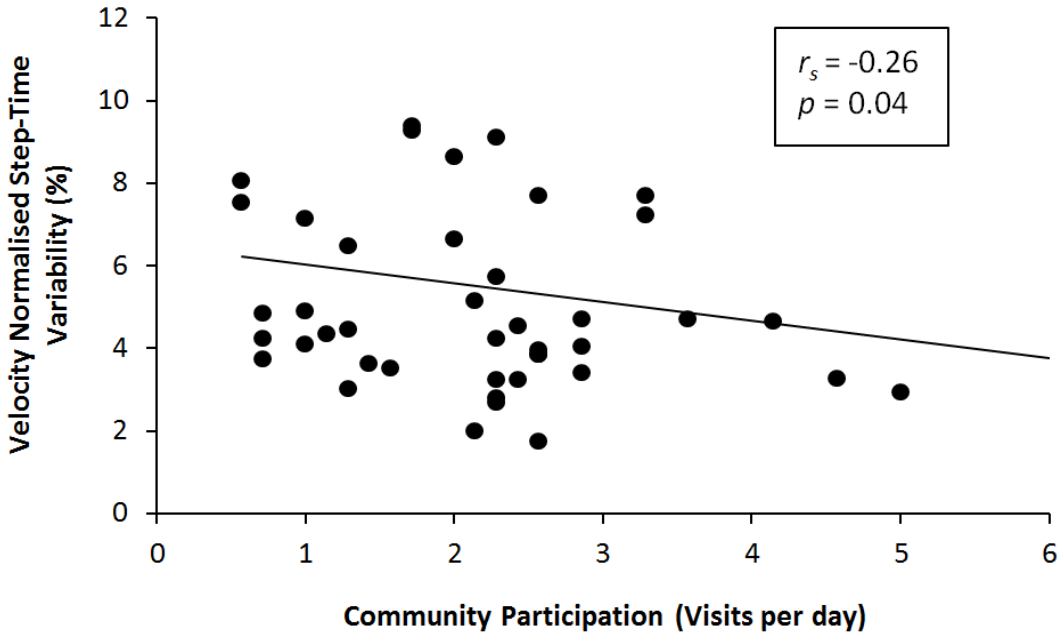

Figure 6.5: The association between clinically assessed step-time variability and community participation. Greater normalised step-time variability was associated with reduced community participation.

Falls history was obtained for 45 participants, with two participants unable to recall falls history (one of the two was also excluded due to failing to charge the GPS device). Sixteen (36%) amputees had reported experiencing a fall in the preceding 12 months. The characteristics of the fallers and non-fallers are summarised in table 6.4. There were no significant differences between fallers and non-fallers for age, gender, indication for amputation, time since amputation, K-level, or AMP-PRO score (all $p > 0.08$). There was a significant difference for employment status for fallers and non-fallers ($X^2_{(1)} = 4.51$, $p = 0.05$) as amputees with history of falls were less likely to be employed (see table 6.4). There was a significant difference between fallers and non-fallers for commercial activity ($t_{(43)} = 2.12$, $p = 0.04$), recreational activity ($t_{(43)} =$

1.99, $p = 0.05$) and total community activity ($t_{(43)} = 2.56$, $p = 0.01$). There were no significant differences between fallers and non-fallers for activity in employment roles, residential, health, social, other or the home setting (all $p > 0.27$). There was a significant difference between fallers and non-fallers for recreational participation ($t_{(43)} = 2.07$, $p = 0.04$) and total community participation ($t_{(43)} = 2.08$, $p = 0.04$). There were no significant differences between fallers and non-fallers for participation in employment roles, residential, commercial, health, social or other (all $p > 0.25$). Community activity and participation data are provided in tables 6.5 and 6.6 respectively.

Table 6.4: Demographics and clinical characteristics between fallers and non-fallers.

Demographics and Clinical Characteristics	Faller (n = 16)	Non-Faller (n = 29)	Statistic
Age (years, mean (SD))	64.4 (13.5)	58.5 (13.3)	$p = 0.17$
Gender (n (%) male)	10 (63%)	25 (86%)	$p = 0.08$
Indication for amputation, n(%)			$p = 0.51$
PVD	9 (56%)	8 (31%)	
Trauma	6 (38%)	11 (28%)	
Other	1 (6%)	10 (26%)	
Time since amputation (years, mean (SD))	13.2 (19.1)	18.0 (19.2)	$p = 0.20$
K-Level (n (%))			$p = 0.13$
K-1	1 (6%)	0 (0%)	
K-2	3 (19%)	1 (3%)	
K-3	4 (25%)	9 (31%)	
K-4	8 (50%)	19 (66%)	
AMP-PRO score (mean (SD))	39.6 (7.2)	43.2 (3.0)	$p = 0.23$
Employment status (n (%) employed)	2 (13%)	13 (45%)	$p = 0.05$

PVD, peripheral vascular disease; AMP-PRO, amputee mobility predictor. Other indications for amputation include congenital, infection and tumour.

Table 6.5: Community activity for fallers and non-fallers, separated by participation categories.

Community Categories	**Activity** *Step count per day* **Mean (SD)**		**Statistic**
	Faller	**Non-Faller**	
Employment	2,754 (2,432)	2,268 (2,383)	$p = 0.79$
Residential	335 (497)	392 (434)	$p = 0.69$
Commercial	317 (447)	687 (617)	$p = 0.04$
Health	152 (211)	89 (166)	$p = 0.27$
Recreational	79 (251)	385 (587)	$p = 0.05$
Social	196 (371)	275 (563)	$p = 0.61$
Other	30 (104)	61 (103)	$p = 0.34$
Total community	1,453 (1,535)	2,871 (1,907)	$p = 0.01$
Home	3,445 (2,235)	3,700 (1,982)	$p = 0.69$

Note/ Employment step count and visit is representative of amputees who were employed (n = 15). All other categories were representative of all amputee participants (n = 45).

Table 6.6: Community participation for fallers and non-fallers, separated by participation categories.

Community Categories	**Participation** ***Community visits per day*** **Mean (SD)**		**Statistic**
	Faller	**Non-Faller**	
Employment	1.0 (1.2)	1.6 (1.8)	$p = 0.69$
Residential	0.3 (0.3)	0.4 (0.4)	$p = 0.43$
Commercial	0.6 (0.5)	0.8 (0.5)	$p = 0.25$
Health	0.2 (0.2)	0.1 (0.2)	$p = 0.27$
Recreational	0.1 (0.1)	0.2 (0.2)	$p = 0.04$
Social	0.3 (0.2)	0.3 (0.3)	$p = 0.78$
Other	0.1 (0.2)	0.1 (0.2)	$p = 0.60$
Total community	1.7 (1.1)	2.7 (1.7)	$p = 0.04$

Note/ Employment step count and visit is representative of amputees who were employed (n = 15). All other categories were representative of all amputee participants (n = 45).

6.5 Discussion

This study investigated community activity and participation of transtibial amputees using a simple approach to linking data recorded from separate commercially available accelerometer and GPS devices. Findings from this study demonstrate that data collected from a combination of accelerometer and GPS devices is feasible with a patient group over a seven day period, and the data obtained from these devices had limited interruption due to inadequate GPS signal. Higher functioning (K3 and K4) transtibial amputees demonstrated a wide range of actual community activity and participation levels, which likely contributed to non-significant statistical difference between these functional categories for the measures of community activity and participation. Wearable technology may be a more accurate method of assessing true levels of community activity and participation. In addition, negative relationships were observed between clinically assessed measures of gait variability and levels of community activity and participation. Transtibial amputees with a history of falls have reduced community activity and participation compared to amputees without a history of falls. These results underline the importance of clinical falls and gait function assessments in this population to improve overall quality of life.

Community activity and participation are key indicators of successful rehabilitation and intervention effectiveness (Corrigan & McBurney 2008; WHO 2001). Recent advances in wearable technology have provided rehabilitation clinicians easier access to means of quantifying measures of activity and participation for a range of applications (Bonato 2005; Cooper et al. 2010; Duncan, Badland & Mummery 2009; Ouyang et al. 2010; Patel et al. 2012; Rodríguez, Brown & Troped 2005; Shoval et

al. 2011; Terrier et al. 2000). For amputee rehabilitation, wearable technology may be clinically appropriate to aid prosthetic prescription and to guide rehabilitation interventions. Similar data has been used previously in a case study (Jayaraman et al. 2014), however this study appears to be the first to report linked accelerometer and GPS data in a cohort of transtibial amputees. The methodology presented here may be transferable to other patient populations. The accuracy of wearable GPS devices integrated with geographic information allowed recording of a range of categorised community participation events. Linked SAM and GPS data provided an opportunity to analyse step counts in these categorised locations, and in the community in general, as a measure of community activity. Here it was demonstrated amputees performed a high proportion of activity within the home. For community based activity, the majority was performed in the work place for those amputees who were employed, and the most common community participation was visiting commercial facilities (shopping centres and local shops). The selection of participation events was based on typical activities of amputees, but could be modified and adapted for various patient populations as required. Although GPS devices have potential use in rehabilitation and research of clinical populations there are technical limitations. Primarily, GPS devices rely on satellite signal and have limited capacity for indoor use (Kerr, Duncan & Schipperjin 2011). Data from this study demonstrates that a small proportion (6.5%) of data recording were lost from the GPS data due to insufficient satellite signal which occurred as a result of monitoring everyday activities in this cohort of amputees. This small proportion compares well to previous activity monitoring studies in stroke which report acceptable GPS data loss of 13% (McCluskey et al. 2012).

Community activity and participation data from linked SAM and GPS devices demonstrated that amputees categorised as K1 or K2 performed at lower community activity and participation levels than amputees categorised as either K3 or K4. This finding is not unexpected given that these higher functioning amputees had higher rates of employment. Interestingly there was no statistical difference in community activity and participation between amputees categorised as K3 and K4, most likely due to the wide range of community activity and participation levels within these two groups. This may be surprising given the discrepancies in employment status between these two groups. A potential reason for this lack of significant difference in community activity and participation between K3 and K4 amputees relates to properties of this assessment. There are no subcategories within each K level. Therefore, the difference between a high level K3 and low level K4 are likely to be minimal. Conversely, the differences between a low K3 and a high K4 may be quite large in comparison. Additionally, this system was developed to predict prosthetic requirements of amputees based on their likely requirements in the community. These categories provide indication of the most suitable prosthetic componentry, and do not reflect actual performance. Therefore, these findings may indicate that the predictive K level categories may not reflect actual community activity and participation levels.

Previous literature suggests age (Davies & Datta 2003; Hamamura et al. 2009; Sansam et al. 2009; Schoppen et al. 2003), comorbidities (Hamamura et al. 2009; Schoppen et al. 2003) and indication for amputation (Hamamura et al. 2009) to be factors potentially limiting amputees to perform functionally in the community. Differences in age were found between the K1/2 and K4 amputees. It was expected

to find these differences as previous studies indicate that lower functioning amputees are typically older (see chapter three of this thesis). Therefore, the functional differences between K1/2 and K4 amputees may be a combination of lower functional abilities and older age. However, this study was unable to demonstrate difference between K3 and K4 amputees for both age and indication for amputation suggesting these factors have not limited performance of K4 amputees in the community. Further research in a larger cohort of amputees should be undertaken to decipher implications of these findings and investigate why amputees categorised as K3 and K4 perform functionally similarly in terms of community activity and participation. Higher functioning amputees may require objective community measures (such as accelerometers of GPS devices) to more accurately determine differences in functional abilities, rather than commonly adopted clinical measures (i.e., K levels).

This study further demonstrated the importance of assessing amputee gait function. Levels of community activity and participation were shown to be associated with clinically assessed gait variability. Although the strength of the associations was not strong, the results do suggest that gait variability has potential implications for community activity and participation. It has previously been identified that gait variability is associated with decreased walking confidence, fear of falling, a reduction in daily physical activities and social function (Hausdorff, Rios & Edelberg 2001; Reelick et al. 2009) in older adults. However, this is the first study in an amputee population to identify that higher levels of gait variability are associated with reduced levels of community activity and participation. In chapter five it was identified that amputees with a history of falls have greater gait variability, and it is

therefore likely that many amputees would experience a fear of falls, restricting willingness to mobilise in the community and limiting community participation. Falls are a significant adverse event and many negative consequences of experiencing a fall are well documented. For example, falls are often associated with institutionalisation, hospitalisation, injury, immobilisation and impose a significant cost on the health care system (Stevens et al. 2006; Tinetti & Williams 1997). For older adults falls have been linked to decreased mobility, reduced independence, diminished confidence and self-restriction of community activity (Howland et al. 1998; Tinetti et al. 1994b; Vellas et al. 1997). However, this study advances these findings by demonstrating that a history of falls is associated with reduced community activity and participation for transtibial amputees. Conversely, activity within the home setting was similar between groups. It is likely this reflects increased confidence of the faller group within a familiar setting. This is despite the home setting being the most common location of falls in older adults (Berg et al. 1997). Whilst overall community activity and participation levels were significantly lower in amputees with a history of falls, it appears activity in recreation and commercial areas, and participation in recreation roles were specifically reduced in this group. It should be expected that reduced recreational participation in the community would result in reduced activity levels, however it is interesting to observe that commercial activities were reduced in fallers while participation in this category was similar between groups. This indicates fallers do still participate in attending commercial facilities, potentially to perform tasks such as grocery shopping, however the activity performed in these locations is reduced. It is also surprising that amputees with a history of falls do still participate in social activities, indicating some level of community integration. However, it was somewhat expected

that no differences would be observed in health related activity and participation given similar demographics and clinical characteristics between fallers and non-fallers. In addition, a longer study period may be required to elucidate differences in this community category as the current seven day period may not capture all regular health related activities. Future studies may be required to investigate why amputees with a falls history selectively participate at lower levels in commercial and recreational facilities. Nevertheless, given the prevalence of falls observed in this study (36%), and also reported previously (Miller, Speechley & Deathe 2001), these findings further emphasise importance of clinical falls assessment for lower-limb amputees. Not only is there likely to be some form of physical or psychological injury resulting from a fall (Gooday & Hunter 2004), but evidence from the current study demonstrates fallers achieve suboptimal levels of community activity and participation, and may therefore not successfully achieve the rehabilitation goal of functional mobility (Sansam et al. 2009). Findings from this study may be used to target interventions aiming to reduce falls or increase community activity and participation. For example, future studies may investigate promoting increased activity and participation in recreational and commercial facilities for amputees with a falls history. Similarly, balance and gait interventions to reduce falls risk should consider assessment of quality of life and community integration.

Many factors, apart from falls history, may contribute to differences in levels of community activity and participation assessed in this study. However, results have demonstrated that demographics and clinical characteristics including age, gender, indication for amputation, and time since amputation were not different between fallers and non-fallers. While it is acknowledge that this study has only demonstrated

a relationship between community activity and participation and falls history, the strong results presented here do warrant further consideration. Future studies using a prospective design may seek to determine if experiencing a fall contributes to reduced levels of community activity and participation, or alternatively, if reduced levels of community activity and participation predispose an amputee to experiencing a fall potentially due to reduced mobility confidence or endurance.

There are several limitations to this study which should be acknowledged. First, due to lost GPS signal, 5.3% of the step count data were lost in the data linkage procedure. Although this percentage is low, it may represent a potential bias in this procedure and subsequent data analysis. Second, the data linkage procedure may limit the clinical usefulness of this methodology. However, these results demonstrate a high correlation with total step count and the measure of community activity, and a moderate correlation with total step count and the measure of community participation. Third, the measure of community participation adopted may not completely encompass all aspects of community participation as described by the International Classification of Functioning, Disability and Health (WHO 2001). For example, employment, social and recreational roles may be fulfilled from within a person's home, and therefore the exclusion of this data may not accurately represent community participation. However, a recent review summarised community participation as involvement in activities that occur outside the home, or involve a non-domestic nature (Chang, Coster & Helfrich 2013). Further, participation in activities outside the home present greater mobility and social challenges, and are likely to represent greater community integration. Fourth, this study may also have benefited from inclusion of a participant diary to record daily community activity

and participation. Although participation events were confirmed verbally with participants where required, it has previously been reported that a diary should be included in these studies to aid confirmation of activities, despite accuracy of diary recorded information being inferior to GPS recorded data (McCluskey et al. 2012; Stepien et al. 2007). Inclusion of a travel diary may have aided information recall in these instances. Fifth, results of this study with unilateral transtibial amputees may not be generalisable to other amputee populations, and further investigation is required to determine activity and participation of individuals with different levels of amputation; Finally, amputees recruited to participate in this study were primarily higher functioning (K3 and K4), with a relatively high percentage of traumatic amputees, and lower percentage of vascular amputees compared to that normally found in prosthetic rehabilitation services (see chapter four of this thesis). This is likely due to the long post-operative period in this study, and the poor mortality rates following rehabilitation for vascular amputees (Bhangu, Devlin & Pauley 2009). These results may not accurately reflect lower functioning K1 amputees, or more recent amputees. Despite this, relatively low activity levels amongst recruited amputees were still observed.

6.6 Conclusions

This study demonstrated a simple methodology to link step count and GPS data to assess community activity and participation in a group of unilateral transtibial amputees. The combination of step count data and GPS appears a feasible method to accurately assess community activity and participation. The association identified between community activity and participation and clinical assessments (gait variability and falls history) further highlight the significance of these assessments as

measures related to quality of life. Clinicians should consider potential implications that gait and falls assessments may have on community integration. These assessments may be important markers to monitor during prosthetic rehabilitation.

CHAPTER SEVEN: CORTICOMOTOR EXCITABILITY ASSOCIATION WITH GAIT VARIABILITY IN TRANSTIBIAL AMPUTEES

About this chapter:

Previous chapters identified that speed normalised spatial-temporal gait variability is a sensitive measure of gait function in transtibial amputees. Greater gait variability was associated with a history of falls and decreased community activity and participation. This chapter investigated corticomotor excitability in 20 community dwelling amputees (30% vascular disease). The balance in corticomotor excitability between hemispheres was determined, and the relationship with gait function investigated. This chapter sought to address the research question 'Can TMS measures be used as neurophysiological biomarkers of gait function?' Given evidence supporting bilateral cortical reorganisation following amputation, measures of bilateral corticomotor excitability may be important neurophysiological biomarkers of gait function. Participants in this study were a subset of those recruited for the study in chapter six. Results of this study have been published in the *European Journal of Neuroscience.*

7.1 Abstract

Ipsilateral M1 reorganisation after unilateral lower-limb amputation may degrade function of the amputated limb. It was hypothesised that unilateral lower-limb amputees would have a bilateral increase in corticomotor excitability and increased excitability of ipsilateral M1 would be associated with increased gait variability. Twenty transtibial amputees (16-male) aged 60.1 (range 45-80) years, and twenty age- and gender-matched healthy adult controls were recruited. Single-pulse transcranial magnetic stimulation assessed corticomotor excitability. Two indices of corticomotor excitability were calculated. An index of corticospinal excitability determined relative excitability of ipsilateral and contralateral corticomotor projections to spinal motoneurons innervating the rectus femoris muscle of the amputated limb. A laterality index assessed relative excitability of contralateral projections from each hemisphere. Spatial-temporal gait analysis was performed to calculate step-time, step-length and step-width variability of the amputated limb. Amputees had lower index of corticospinal excitability values, indicating relatively greater excitability of ipsilateral corticomotor projections than controls ($p = 0.04$). Lower index of corticospinal excitability values were associated with increased step-time variability ($p = 0.04$). This association suggests corticomotor projections from ipsilateral M1 to spinal motoneurons innervating the amputated limb rectus femoris muscle may interfere with gait. Cortical excitability in amputees was not increased bilaterally, contrary to the hypothesis. There was no difference in excitability of contralateral M1 between amputees and controls ($p = 0.10$) and no difference in laterality index ($p = 0.71$). It appears both hemispheres control one rectus femoris muscle with predominance of contralateral corticomotor excitability in healthy

adults. Following lower-limb amputation, putative ipsilateral corticomotor excitability is relatively increased in some amputees and may negatively impact on function.

7.2 Introduction

Bipedal locomotion is the quintessential form of ambulation mastered by humans early in life. Activation of M1 of both cortical hemispheres is essential for lower-limb motor control (Luft et al. 2002; Sahyoun et al. 2004), and amputation presents a unique challenge to the bi-hemispheric control of gait. Interestingly, it appears there is bilateral reorganisation of M1 following amputation (Schwenkreis et al. 2003). Reorganisation of M1 contralateral to the side of amputation ($M1_{CON}$) increases cortical excitability and is well characterised (Chen et al. 1998a; Cohen et al. 1991; Fuhr et al. 1992; Hall et al. 1990; Kew et al. 1994). A concomitant increase in corticomotor excitability ipsilateral to the side of amputation ($M1_{IPSI}$) has not been thoroughly investigated. How a bilateral increase in M1 excitability might affect gait in lower-limb amputees is an important question for amputee rehabilitation given the challenges with prosthetic gait and risk of falls (Miller, Speechley & Deathe 2001; Pauley, Devlin & Heslin 2006). The relationship between M1 excitability and function has not been addressed in studies to date. The spatial-temporal parameter, step-time variability, is a measure indicative of falls risk in older adults (Brach et al. 2010; Verghese et al. 2009) and transtibial amputees (Parker, Hanada & Adderson 2013). In chapter five it was identified that variability measures of step-time, step-length and step-width were greater in amputees with a history of falls. There is little understanding regarding cortical contributions to gait variability in the healthy population or how amputation affects cortical excitability and gait variability in amputees.

Bilateral cortical reorganisation is not unique to amputees. Interhemispheric imbalance from suppression of the ipsilesional and facilitation of the contralesional hemisphere controlling the paretic upper-limb in chronic stroke is associated with poor recovery (Grefkes et al. 2008; Murase et al. 2004; Shimizu et al. 2002). Assessing brain neurophysiology with TMS can identify hemispheric imbalance and quantify its impact on function. A laterality index (LI) of contralesional to ipsilesional excitability recorded from the non-paretic and paretic limbs respectively is one method (Brouwer & Schryburt-Brown 2006; Wang et al. 2012). A ratio of contralesional to ipsilesional corticomotor projections to the paretic lower-limb, the index corticospinal excitability (ICE) is another. In the latter, upregulation of ipsilateral corticomotor projections from the contralesional hemisphere is associated with poor lower-limb control in stroke (Jayaram et al. 2012; Madhavan, Rogers & Stinear 2010). The rationale for this current study was that a similar upregulation of ipsilateral projections to the amputated limb would degrade gait in lower-limb amputees. The primary aim was to investigate bilateral corticomotor excitability in healthy adults and lower-limb amputees using two neurophysiological indices, the LI and ICE. The secondary aim was to assess if there was an association between neurophysiological indices and gait function. It was hypothesised that lower-limb amputees would have a bilateral increase in corticomotor excitability and greater excitability of putative ipsilateral corticomotor projections would be associated with increased gait variability, indicating reduced function.

7.3 Materials and Methods

7.3.1 Participants

Twenty unilateral transtibial amputees (16 male), with mean age of 60.1 years (range 45-80), and 21.7 (SD 22.3) years since amputation were recruited. The AMP-PRO was used to determine function and categorise K levels (Gailey et al. 2002). Higher K level scores indicate greater function (range K1-K4). Description of K levels is as follows; K1 non-community ambulator, K2 limited community ambulator, K3 unlimited community ambulator, and K4 high functioning ambulator (Gailey et al. 2002). Amputees of K1 level were excluded from the study as they were unable to perform functional gait assessment. A comparator group of 20 age and gender matched healthy adults were purposively recruited as control participants (mean age 59.3 years (range 43-83)). Upper and lower-limb dominance was assessed with the Edinburgh Handedness Inventory (Oldfield 1971) and in control participants the non-dominant limb was modelled as the amputated limb. Lower-limb dominance for amputees was retrospectively recalled prior to the amputation. Amputee and control participant demographics and clinical characteristics are summarised in table 7.1. Potential participants with contraindications for TMS, including those with metallic implants, a history of seizures and medications known to alter central nervous system excitability were excluded (Rossi et al. 2009) following screening by a rehabilitation physician. Ethical approval was provided by the Southern Adelaide Clinical Human Research Ethics Committee and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Table 7.1: Participant demographics and clinical characteristics.

Amputee Participants									Control Participants				
Age	Sex	Dom Limb	Indication	Time Amp	Amp Side	ICE	LI	K Level	Age	Sex	Dom Limb	ICE	LI
50	M	Right	Trauma	15.5	Left	0.40	0.01	4	50	M	Right	0.75	0.56
61	M	Right	Trauma	42.7	Right	0.92	0.54	4	60	M	Right	0.91	0.24
49	M	Right	Trauma	31.3	Right	0.08	0.42	4	51	M	Right	0.50	-0.10
64	M	Left	Trauma	3.7	Left	-0.50	0.29	4	66	M	Right	0.69	0.18
57	M	Right	Infection	53.9	Right	0.80	-0.33	4	57	M	Right	0.86	-0.18
80	M	Right	Tumour	57.7	Left	0.22	-0.92	4	83	M	Right	0.28	-0.23
65	M	Right	Other	7.2	Left	0.37	-0.55	4	66	M	Right	0.38	-0.09
60	M	Right	Trauma	20.9	Right	-0.13	-0.53	2	59	M	Left	0.26	0.60
61	M	Right	Other	1.5	Right	-0.14	-0.47	4	60	M	Right	0.63	-0.59
55	M	Right	PVD	5.0	Left	0.58	-0.74	4	53	M	Right	0.05	-0.34
61	M	Right	Trauma	59.7	Left	0.60	-0.11	4	59	M	Right	0.94	0.46
51	M	Right	PVD	0.7	Right	0.11	0.17	4	52	M	Right	0.33	-0.07
67	M	Right	PVD	6.4	Left	0.54	-0.35	3	67	M	Left	0.09	-0.82
45	M	Right	Trauma	9.2	Right	0.58	-0.14	4	43	M	Right	0.01	-0.71
61	M	Right	Trauma	41.6	Right	0.18	0.48	4	64	M	Right	0.66	0.68
55	M	Right	PVD	0.8	Left	0.63	0.39	3	54	M	Right	0.55	-0.06

53	F	Right	Trauma	17.0	Right	-0.15	-0.55	3	53	F	Right	0.26	-0.28
60	F	Right	Congenital	57.8	Right	0.11	-0.34	4	59	F	Right	0.45	-0.14
68	F	Right	PVD	1.1	Right	-0.09	0.61	3	60	F	Right	0.46	0.27
78	F	Right	PVD	0.9	Right	0.06	0.41	2	70	F	Right	0.40	-0.02

Dom Limb, dominant limb; Time Amp, time since amputation; Amp Side, side of amputation; ICE, index of corticospinal excitability; LI, laterality index; M, male; F, female; PVD, peripheral vascular disease.

Age and time since amputation are reported in years.

Indication of 'Other' includes undetected medical condition, and blood clot in limb.

Note, There were no differences between upper and lower-limb dominance for any participant. K Levels indicate amputee functional ability. K2 is a limited community ambulator who has ability to traverse low level environmental barriers such as curbs, stairs or uneven surfaces; K3 is a community ambulator capable of traversing most environmental barriers and is capable of ambulation with variable cadence; K4 is a ambulator capable of high impact, stress or energy levels and is typical of an active adult or athlete.

7.3.2 Protocol

Participants attended a single session to assess brain neurophysiology and spatial-temporal gait parameters. During TMS participants were seated comfortably with hip and knee joints flexed to 90°. A seated knee-extension task was used to unilaterally pre-activate the rectus femoris (RF) prior to each TMS pulse in response to an auditory cue repeated at 0.2Hz intervals. Consistent muscle activation at 10-15% maximal voluntary contraction was achieved by monitoring visual feedback of raw electromyography (EMG) signal from the RF. Transcranial MS pulses were triggered during muscle contractions using Signal software (v5.09).

7.3.3 Electromyography

Surface EMG was recorded from the RF bilaterally using 10mm-diameter Ag/AgCl electrodes (Ambu, Ballerup, Denmark) placed 2cm apart over the muscle bellies, with the distal electrode approximately 12cm superior to the midpoint of the patella. A 20mm-diameter ground Ag/AgCl electrode (3M Health Care, Canada) was placed over the patella. Prior to affixing the electrodes, hair was removed by shaving, and the top layer of skin lightly abraded for optimal contact. Electromyography signals were sampled at 2000Hz (CED 1401; UK), amplified (CED 1902; UK), band-pass filtered (20-1000Hz) and stored for offline analysis (Signal v5.09).

7.3.4 Transcranial magnetic stimulation

Single-pulse TMS was delivered using a Magstim 200 stimulator (Magstim Company, Dyfed, UK). A flat 70mm wing diameter, figure eight coil was held tangentially over the scalp with the handle pointing 30° posterior-medially in the transverse plane. This coil orientation was determined from extensive piloting. As a

guide, the coil was initially positioned 1cm posterior, 1.5cm lateral to the vertex (Madhavan, Rogers & Stinear 2010). The 'hotspot' for evoking maximal responses in the contralateral active RF was then determined for each M1 by systematically moving the coil over a 1cm grid from this location and marked on the scalp. Active motor threshold (AMT) was determined separately for each M1 as the minimum stimulus intensity eliciting a 100μV MEP in five of ten stimuli in the contralateral RF (Rossini et al. 1994). The stimulus intensity evoking a maximal MEP response (MEP_{MAX}) in the contralateral RF was determined for each M1. Three stimulus-response (S-R) curves were constructed from MEPs recorded at equally spaced intensities between AMT and MEP_{MAX} (inclusive). Two S-R curves were constructed from MEPs at six different intensities in each RF following stimulation of the respective contralateral M1 (contralateral S-R curves). A third S-R curve was constructed from MEPs recorded in RF of the amputated limb following stimulation of $M1_{IPSI}$ (ipsilateral S-R curve). The ipsilateral S-R curve was constructed with one additional stimulus intensity above MEP_{MAX} to account for higher thresholds to evoke ipsilateral MEPs (Ziemann et al. 1999), which usually equated to 90-95% MSO. For each intensity of the S-R curve, 14 MEPs were collected in random order.

Responses where pre-stimulus root mean square EMG (rmsEMG) were 2 SD above or below the mean were removed prior to averaging (range 0-2) to ensure consistency of MEP responses. From the retained traces, MEPs were measured peak-to-peak, averaged and plotted against stimulus intensity. The slope of the S-R curve was determined from the linear portion by linear regression. A computerised mathematical algorithm was used to determine the steepest section of the S-R curve. The algorithm used a sliding window of different combinations of consecutive points

along the S-R curve (minimum 3, maximum all) to systematically select those that made up the steepest slope (SR_{SLOPE}) (figure 7.1). The SR_{SLOPE} was used to calculate two indices of corticomotor excitability for each participant. First, ICE assessed excitability of contralateral and ipsilateral corticomotor projections to the amputated limb (Madhavan, Rogers & Stinear 2010). Negative ICE values indicate relatively greater excitability of ipsilateral, compared to contralateral, descending corticomotor projections. The equation to calculate ICE was;

$$ICE = \frac{(\text{contralateral } SR_{SLOPE} - \text{ipsilateral } SR_{SLOPE})}{(\text{contralateral } SR_{SLOPE} + \text{ipsilateral } SR_{SLOPE})}$$

Second, a LI was determined to assess excitability of contralateral corticomotor projections innervating the amputated and non-amputated limb respectively. Negative LI values indicate relative greater excitability of contralateral projections to spinal motoneurons innervating RF of the non-amputated limb. Positive LI values indicate relative greater excitability of contralateral projections to spinal motoneurons innervating RF of the amputated limb. The equation to calculate LI was;

$$LI = \frac{(\text{contralateral } SR_{SLOPE}\ M1_{CON} - \text{contralateral } SR_{SLOPE}\ M1_{IPSI})}{(\text{contralateral } SR_{SLOPE}\ M1_{CON} + \text{contralateral } SR_{SLOPE}\ M1_{IPSI})}$$

The ipsilateral silent period (ISP) was used to assess interhemispheric inhibition from stimulation of $M1_{IPSI}$ at 80%MSO (Avanzino, Teo & Rothwell 2007; Chen, Yung & Li 2003; Trompetto et al. 2004). This intensity was chosen because at higher

intensities the onset of the ISP was often masked by the MEP. Data were rectified and averaged and the ISP measured from this average. Ipsilateral SP onset was defined when post-stimulus EMG fell below the mean of the pre-stimulus EMG for a continuous period of 10ms in a window 20-80ms after the stimulus. Ipsilateral SP offset was defined when EMG returned to baseline levels (Avanzino, Teo & Rothwell 2007; Chen, Yung & Li 2003; Trompetto et al. 2004). The ISP was calculated as the area between onset and offset points relative to the mean of the prestimulus rmsEMG (ISP$_{AREA}$), expressed in mV•ms (see figure 7.2).

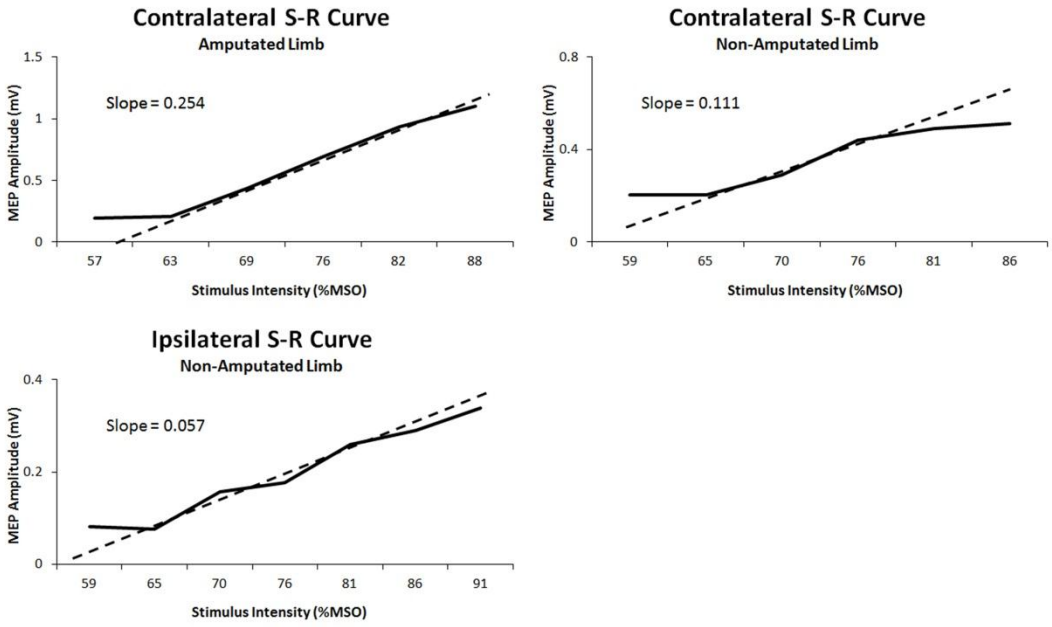

Figure 7.1: A representative example of the three S-R curves from an amputee participant.

SR$_{SLOPE}$ was calculated from the steepest section of the curve (minimum three points, maximum all) using linear regression (represented by the dotted line). ICE and LI for this participant were 0.63 and 0.39 respectively.

MEP, motor evoked potential; mV, millivolts; MSO, maximum stimulator output.

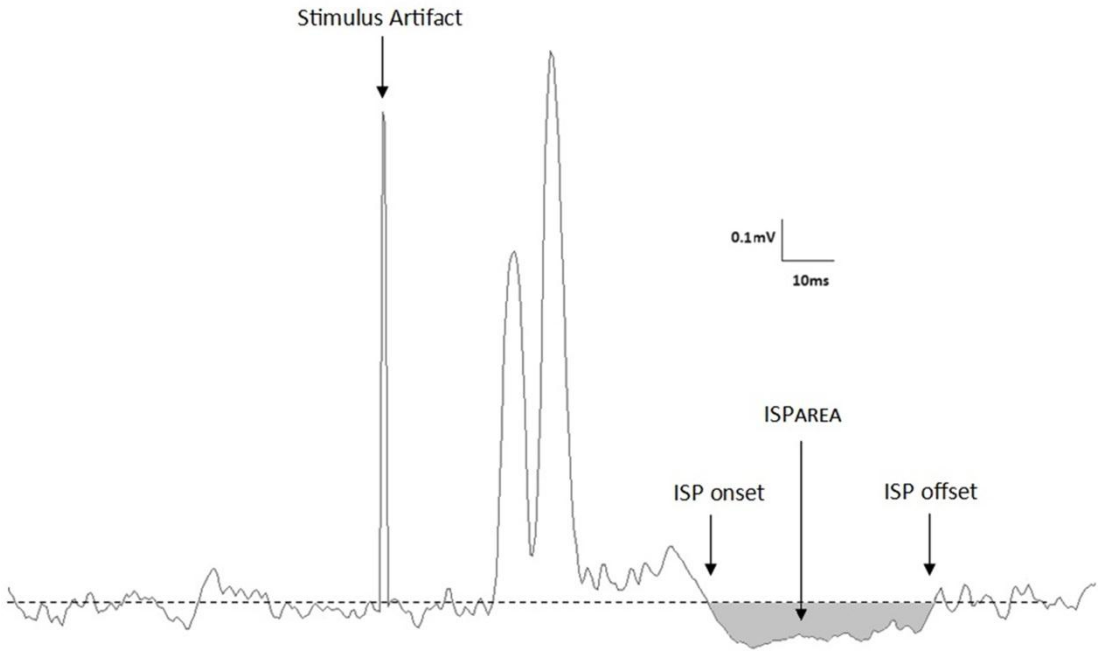

Figure 7.2: Calculation of the ipsilateral silent period

A rectified ipsilateral MEP in a representative amputee participant demonstrating the ISP onset and offset (indicated by the arrows) used to calculate ISPAREA. The trace is the average of 14 MEPs. The grey shaded area indicates ISPAREA.

ISP, ipsilateral silent period.

7.3.5 Spatial-temporal gait variability

Spatial-temporal gait was assessed using an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA) with embedded pressure sensors to capture individual footfall data over an active area 4.9m x 0.6m. Participants completed 10 consecutive passes over the GAITRite at their self-selected comfortable walking speed. Data were sampled at 120Hz and analysed using GAITRite software (version

4.5.5). Variability of spatial-temporal parameters was assessed by the CV, calculated as SD divided by the mean expressed as a percentage. The primary gait outcome measures, step-time, step-length and step-width variability are speed dependent parameters and greater variability can occur in raw data with variations in walking speed between trials (Beauchet et al. 2009). Individual gait trial parameters were therefore normalised to walking speed for all participants prior to calculation of CV in accordance with similar previous studies (Hof 1996) (see also chapter 5).

7.3.6 Data analysis

The normality of data were checked with a Shapiro-Wilk test. Post-hoc tests explored significant effects and were corrected for multiple comparisons using a modified Bonferroni correction (Rom 1990). Significance level was set at $p \leq 0.05$ and SPSS software was used for all statistical analyses (IBM corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0).

7.3.6.1 Corticomotor excitability

Differences between amputee and control ICE, LI and ISP$_{AREA}$ were tested with separate independent t-tests. To further understand fundamental contributions of each hemisphere to ICE ratios, SR$_{SLOPE}$ and MEP latencies were separately analysed using one-way ANOVAs. The four independent variables were; amputee contralateral, amputee ipsilateral, control contralateral, control ipsilateral. To understand how the contralateral and ipsilateral SR$_{SLOPE}$ contributed to ICE in amputees, correlation analysis was performed between ICE and ipsilateral SR$_{SLOPE}$, ICE and contralateral SR$_{SLOPE}$, and between the ipsilateral and contralateral SR$_{SLOPE}$ used in the ICE calculations. To further understand fundamental

contributions of each hemisphere to LI ratios, SR_{SLOPE} and MEP latencies were separately analysed using one-way ANOVAs. The four independent variables were; amputee amputated and non-amputated limb, control dominant and non-dominant limb. Background EMG was compared across the two contralateral S-R curves with a 2 group (amputee, control) x 6 condition (S-R curve intensities) ANOVA. Similarly a 2 group (amputee, control) x 7 condition (S-R curve intensity) ANOVA was used for the ipsilateral S-R curve.

7.3.6.2 Functional gait variability

Gait variability measures (step-time, step-length, step-width) were normalised with log (10) transformations. Square-root, reciprocal and exponential transformations were also investigated, but only log (10) transformations normalised all data. Gait variability measures normalised to walking speed were assessed between amputees and controls with separate independent t-tests.

7.3.6.3 Corticomotor excitability and gait function

Linear regression models analysed association between the primary corticomotor excitability measures (ICE, LI) and gait variability (step-time, step-length, step-width normalised with log(10) transformation) and were controlled for factors known to influence gait (age, time since amputation, stump length and indication for amputation) (Callisaya et al. 2010; Gailey et al. 1994; Gonzalez, Corcoran & Reyes 1974; Kang & Dingwell 2008; Mâaref et al. 2010).

7.4 Results

No adverse events were experienced during TMS or gait analysis.

7.4.1 Corticomotor excitability measures

Corticomotor excitability measures are summarised in table 7.2. Amputees had smaller ICE values than controls ($t_{(38)} = 2.07$, $p = 0.04$). Five amputees had negative ICE values, while no controls had negative ICE values. There were no significant differences between amputees and controls for LI ($p = 0.71$) or ISP$_{AREA}$ ($p = 0.42$). The one-way ANOVA to elucidate fundamental contributions to the ICE ratio found a difference in SR$_{SLOPE}$ ($F_{(3,76)} = 4.55$, $p = 0.006$). Post-hoc analysis revealed amputees had steeper ipsilateral SR$_{SLOPE}$ ($t_{(38)} = 1.96$, $p = 0.03$), but not contralateral SR$_{SLOPE}$ ($p = 0.10$) compared to control subjects. As expected, contralateral SR$_{SLOPE}$ was steeper than ipsilateral SR$_{SLOPE}$ for both amputees ($t_{(19)} = 3.07$, $p = 0.006$) and controls ($t_{(19)} = 4.52$, $p = 0.001$). There were differences in MEP latency ($F_{(3,76)} = 6.05$, $p = 0.001$), with post-hoc analysis revealing ipsilateral MEP onset latency was 1.5ms longer than contralateral MEP onset latency for both amputees ($t_{(19)} = 3.03$, $p = 0.004$) and controls ($t_{(19)} = 2.98$, $p = 0.005$). Relative contributions of SRslope to smaller ICE ratios in amputees were analysed. There was no correlation between ICE and contralateral SR$_{SLOPE}$ ($p = 0.17$) or ICE and ipsilateral SR$_{SLOPE}$ ($p = 0.48$). There was a significant positive correlation between ipsilateral SR$_{SLOPE}$ and contralateral SR$_{SLOPE}$ ($r = 0.76$, $p = 0.001$) (see figure 7.3). The one-way ANOVA to elucidate fundamental contributions to the LI ratio showed a difference in SR$_{SLOPE}$ ($F_{(3,76)} = 2.60$, $p = 0.05$). Post-hoc analysis revealed contralateral SR$_{SLOPE}$ evoked from stimulation of M1$_{IPSI}$ to be steeper in amputees than controls ($t_{(38)} =$

1.70, $p = 0.04$). SR_{SLOPE} evoked from stimulation of $M1_{CON}$ was no different between amputees and controls ($p = 0.10$). There was a difference in MEP latency ($F_{(3,76)} = 3.43$, $p = 0.02$), with post-hoc analysis revealing amputee MEP latency measured on the amputated limb to be shorter than the non-amputated limb ($t_{(38)} = 2.46$, $p = 0.02$). There was no difference in MEP latency between sides for control subjects ($p = 0.98$). For amputees average background EMG for the amputated limb contralateral S-R curve was 0.04mV (SD 0.03), non-amputated limb contralateral S-R curve was 0.06mV (SD 0.05), and ipsilateral S-R curve was 0.04mV (SD 0.02). For controls average background EMG for the non-dominant limb contralateral S-R curve was 0.05mV (SD 0.02), dominant limb contralateral S-R curve was 0.04mV (SD 0.02), and ipsilateral S-R curve was 0.04mV (SD 0.02). There were no main effects of group (all $p > 0.12$) or intensity (all $p > 0.99$) for background EMG.

Table 7.2: Cortical excitability measures compared between amputee and control participants.

Cortical Excitability Measure	Amputee Mean(SD)	Control Mean(SD)	Statistic
Con SR_{SLOPE} $M1_{CON}$	0.38 (0.39)	0.25 (0.20)	$p = 0.10$
Con SR_{SLOPE} $M1_{IPSI}$	0.61 (0.77)	0.30 (0.27)	$p = 0.04$*
Ipsi SR_{SLOPE} $M1_{IPSI}$	0.21 (0.27)	0.09 (0.09)	$p = 0.03$*
ICE	0.26 (0.37)	0.47 (0.28)	$p = 0.04$*
LI	-0.09 (0.47)	-0.03 (0.42)	$p = 0.71$
ISP_{AREA} (mV·ms)	0.53 (0.38)	0.64 (0.50)	$p = 0.42$

* significant at $P \leq 0.05$;

Con, contralateral; Ipsi, ipsilateral; M1CON, primary motor cortex contralateral to the amputated limb; M1IPSI, primary motor cortex ipsilateral to the amputated limb; ICE, index of corticospinal activity; LI, laterality index; MEP, motor evoked potential; ISP, ipsilateral silent period.

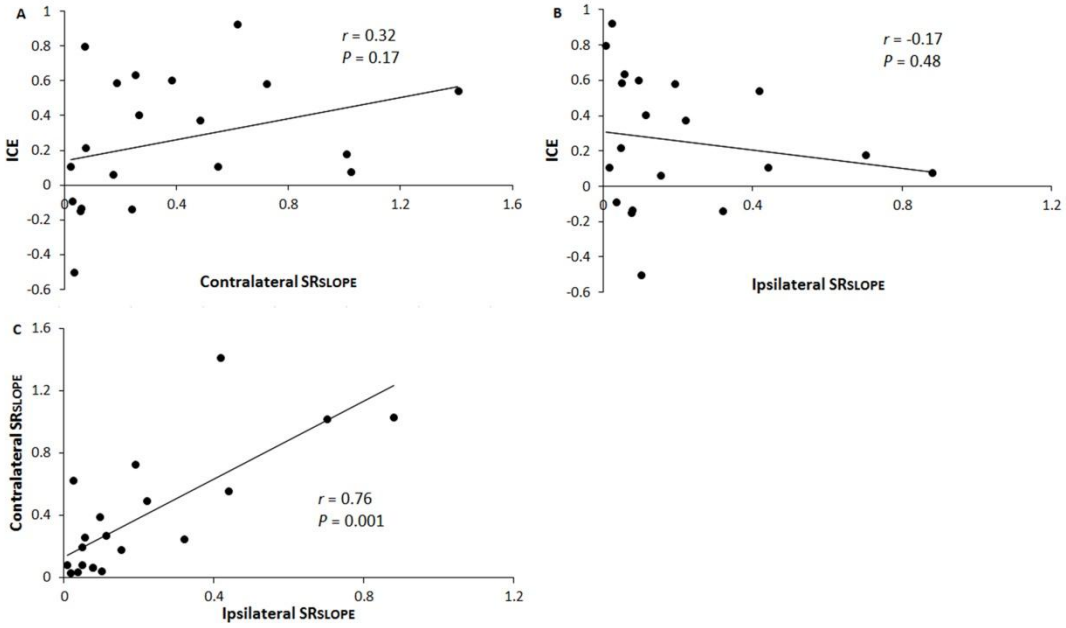

Figure 7.3: Correlation analysis to determine relative contributions of contralateral and ipsilateral SRSLOPE to ICE.

Figure A and B illustrate that there was no correlation between contralateral SRSLOPE and ICE, or ipsilateral SRSLOPE and ICE. Figure C illustrates a positive correlation between contralateral SRSLOPE and ipsilateral SRSLOPE.

ICE, index of corticospinal excitability; SRSLOPE, slope values of the S-R curve.

7.4.2 Functional gait variability

For amputees normalised step-time variability was 5.15% (SD 3.4), step-length variability was 2.62% (SD 1.5) and step-width variability was 12.1% (SD 4.1) on the

amputated limb. For control participants normalised step-time variability was 4.61% (SD 1.7), step-length variability was 2.54% (SD 1.3), and step-width variability was 10.7% (SD 6.3) on the non-dominant limb. There were no significant differences in gait variability (all $p > 0.41$).

7.4.3 Corticomotor excitability and gait function

For amputees, linear regression models controlling for age, time since amputation, stump length and indication for amputation demonstrated a negative relationship between ICE and step-time variability on the amputated limb ($R^2 = 0.64$, $p = 0.04$) (see figure 7.4). No other independent variables controlled for were significant ($p > 0.12$).. There was no significant relationship between ICE and step-length variability ($p = 0.08$) or step-width variability ($p = 0.47$). There was no relationship between LI and any gait variability measures (all $p > 0.51$). For control subjects there were no relationships between ICE or LI and normalised gait variability measures on the non-dominant limb ($p > 0.77$) (see figure 7.5).

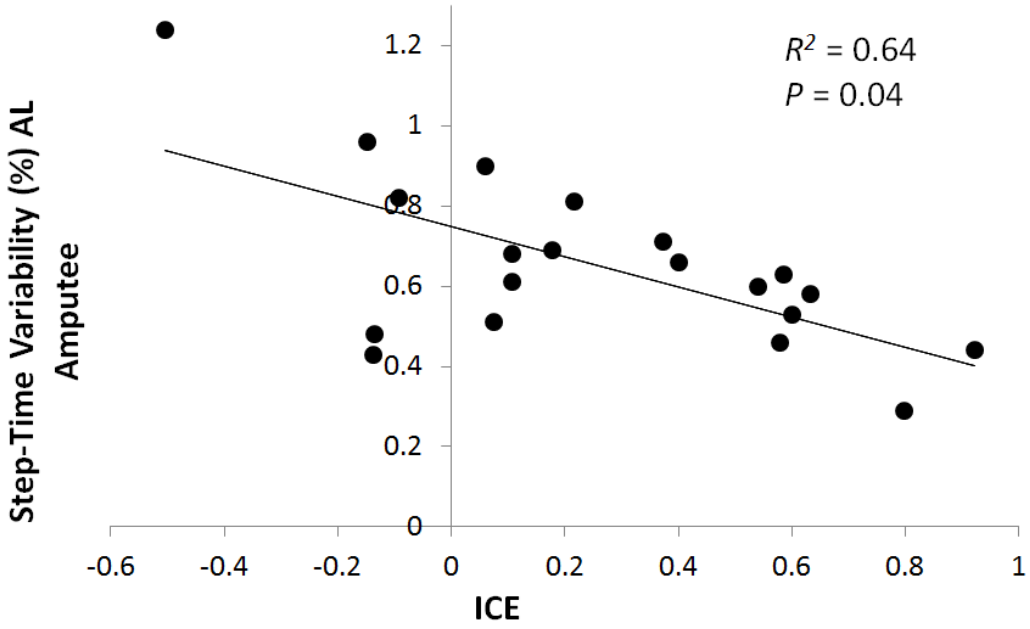

Figure 7.4: Linear regression analysis of step-time variability normalised to walking speed (log (10) transformed) and ICE for amputees.

ICE, index of corticospinal excitability; AL, amputated limb.

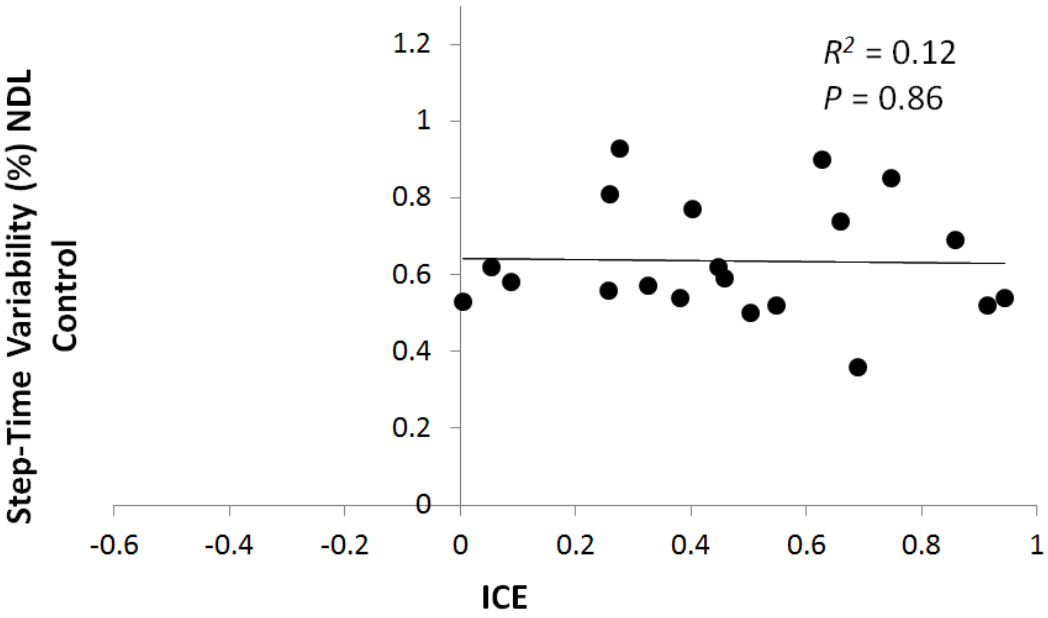

Figure 7.5: Linear regression analysis of step-time variability normalised to walking speed (log (10) transformed) and ICE for control subjects.

ICE, index of corticospinal excitability; NDL, non-dominant limb.

7.5 Discussion

This study investigated bilateral corticomotor excitability and gait variability in healthy adults and unilateral transtibial amputees. There were several findings with relevance for corticomotor control of the lower-limb and the effect of lower-limb amputation. In healthy adults there was bilateral cortical control of one rectus femoris muscle, with predominance of contralateral over ipsilateral excitability. In some amputees there was a change in the relative excitability between the hemispheres whereby greater ipsilateral, relative to contralateral excitability lead to smaller ICE values. Smaller ICE values in amputees were associated with increased step-time variability on the amputated limb. Contrary to the hypothesis, there was no

bilateral increase in corticomotor excitability in amputees as contralateral M1 excitability was no different to controls. The LI was not different between amputees and controls. A summary of the key neurophysiological findings of this study can be found in figure 7.6. The results of this study and their putative implications for amputee rehabilitation are discussed below.

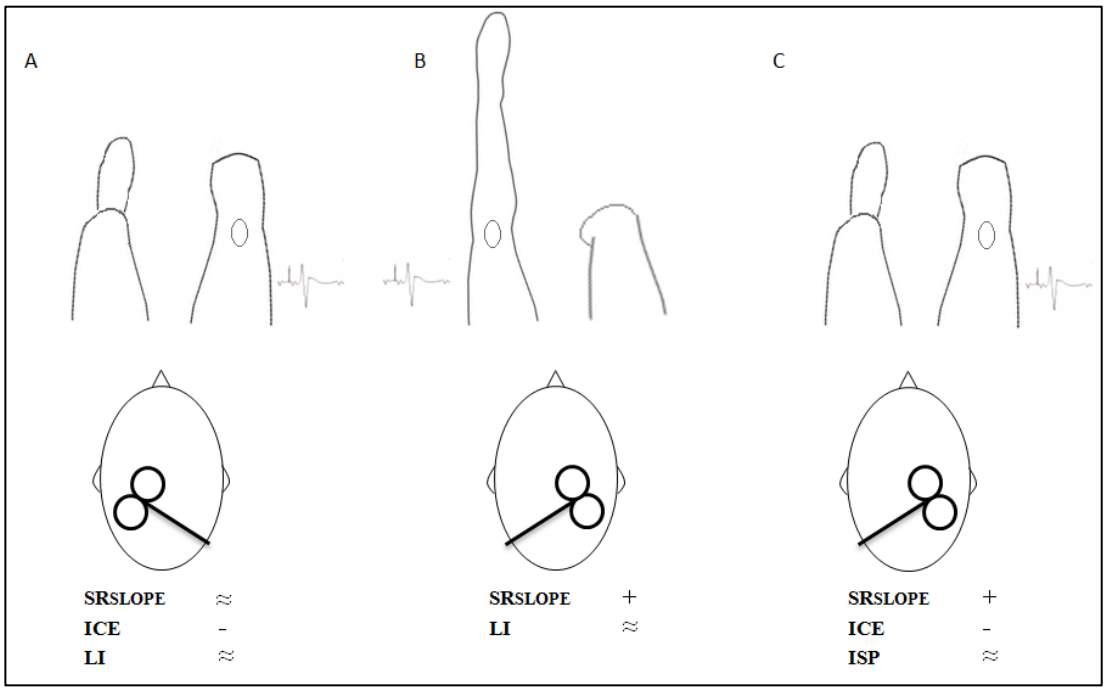

Figure 7.6: A schematic diagram to illustrate the difference in neurophysiological measures between amputees and controls.

The three conditions were A) contralateral MEPs recorded from the activated QM on the amputated limb, B) contralateral MEPs recorded from the activated QM on the non-amputated limb, and C) ipsilateral MEPs recorded from the activated QM on the amputated limb.

≈, no difference between amputees or controls; +, higher values for amputees compared to controls; -, lower values for amputees compared to controls.

SRSLOPE, slope of the stimulus response curve; MEP, motor evoked potential; ICE, index of corticospinal excitability; LI, laterality index; ISP, ipsilateral silent period.

In the current study there was an increase in the ipsilateral SR$_{SLOPE}$ recorded in the rectus femoris muscle of the amputated limb, suggesting greater ipsilateral corticomotor excitability. This conclusion must be interpreted conservatively however. A limitation of the TMS method used in this study is the 'hotspot' for lower-limb muscle representations is adjacent to the interhemispheric fissure, raising the question of whether the coil inadvertently stimulated both hemispheres. Certainly, ipsilateral responses to TMS in the lower-limb are a mix of ipsilateral and contralateral descending inputs as acknowledged previously (Jayaram et al. 2012; Madhavan, Rogers & Stinear 2010). It is difficult to know what proportion of the responses used to calcuate SR$_{SLOPE}$ in the current study were ipsilateral in origin. However, these results indirectly suggest that a good proportion of the ipsilateral response was mediated from projections other than the contralateral corticospinal tract. Ipsilateral responses were greater in amputees while contralateral responses recorded in the same rectus femoris muscle were no different to controls. If the offset coil location for evoking ipsilateral responses was mostly stimulating the contralateral hemisphere, there should have been no difference between groups. Nonetheless, it is difficult to be sure and ipsilateral responses are referred to as 'putative' in the following discussion.

Motor control of the rectus femoris muscle depends upon both ipsilateral and contralateral hemispheres in humans, although it appears predominance of the contralateral hemisphere is normal. Functional MRI studies demonstrate that isolated knee flexion/extension and ankle dorsiflexion/plantar flexion movements activate both ipsilateral and contralateral M1 (Luft et al. 2002; Sahyoun et al. 2004). Transcranial MS findings from this study progress this understanding by

demonstrating a contralateral predominance of cortical excitability, as observed in healthy adults was not associated with gait variability. If following lower-limb amputation putative ipsilateral corticomotor excitability dominated over contralateral, there was an association with increased gait variability. While both hemispheres contribute to the control of human gait, it is evident that the balance of excitability between the M1s is critical for normal function. Unexpectedly there was no bilateral increase in corticomotor excitability in amputees as there was no difference in M1CON excitability between amputees and controls. This was surprising as previous lower-limb amputee studies have reported reorganisation of M1CON in the forms of lower thresholds for TMS (Chen et al. 1998a), larger MEPs (Fuhr et al. 1992), reorganisation of motor maps (Schwenkreis et al. 2003), or a reduction in intracortical inhibition (Chen et al. 1998a). It is not obvious why M1CON excitability was unaffected in this group of amputees, but might relate to factors such as length of time since amputation and their relatively high ambulatory function.While contralateral corticomotor excitability over the non-amputated limb was greater in amputees this did not influence the LI, which did not discriminate between amputees and control participants.

Amputees had smaller ICE values than controls indicating relatively greater putative ipsilateral to contralateral corticomotor excitability. Smaller ICE values could potentially result from a steeper ipsilateral SRSLOPE, or flatter contralateral SRSLOPE. To elucidate which hemisphere contributed to negative ICE values, this study separately correlated each M1 SRSLOPE with ICE. There was no relationship for either hemisphere, indicating negative ICE was not an absolute increase in M1IPSI or decrease in M1CON excitability. Instead it was those amputees with a *relatively*

greater putative ipsilateral to contralateral M1 excitability that demonstrated smaller ICE values. It is also likely that smaller ICE values indicate greater M1IPSI excitability than the suppression of M1CON because the ISP, assessing the degree of interhemispheric inhibition from M1IPSI to M1CON, was similar for amputees and controls. Ipsilateral SPs evoked in the lower-limb are considered to be mediated by interhemispheric pathways similar to the upper-limb (Lo & Fook-Chong 2004). The ISP results, at least in part, from activation of interhemispheric projections across the corpus collosum from the stimulated hemisphere that inhibit the homologous area of the contralateral hemisphere (Chen, Yung & Li 2003; Trompetto et al. 2004). The net result of an increase in interhemispheric inhibition is suppression of corticomotor output from contralateral M1 (Di Lazzaro et al. 1999; Ferbert et al. 1992), evoking a longer ISP, which was not seen in the current study. Finally, increased interhemispheric inhibition would result in a negative LI value which was also not observed. The findings of the present study indicate smaller ICE values in amputees compared to controls likely result from increased excitability of putative ipsilateral descending projections to the spinal cord.

Smaller ICE values in amputees were associated with increased step-time variability for the amputated limb. Increased step-time variability is a predictor of higher falls risk (Brach et al. 2010; Parker, Hanada & Adderson 2013; Verghese et al. 2009). A causal relationship was not tested in the current study. However, the strong association between smaller ICE values and functional measures may indicate that upregulated putative ipsilateral projections degrade function, or alternatively compensatory gait patterns may increase excitability of putative ipsilateral corticomotor projections. Further studies are required to demonstrate cause and

effect, and may prove ICE is a valid neurophysiological marker of reduced function in lower-limb amputees. It is unlikely that smaller ICE values in amputees were a direct result of the clinical characteristics or pathology leading to the amputation as those with negative ICE were a disparate group. This indicates changes in corticomotor excitability were independent of the clinical characteristics or pathology. The pathways responsible for the putative ipsilateral MEPs also cannot be determined from this study, but may involve reticulospinal projections descending to the spinal cord as suggested for the upper-limb following stroke (Ellis et al. 2007; Ellis et al. 2012; Schwerin et al. 2008). Reticulospinal pathways bilaterally innervate axial and proximal spinal motoneurons important for the control and postural support of muscles subserving locomotion (Drew, Prentice & Schepens 2004). Reticulospinal projections branch extensively as they terminate in the spinal gray matter (Matsuyama et al. 1999; Peterson & Abzug 1975), to link widely separated sections of the spinal cord (Lemon 2008). Increased activity in the reticulospinal tract would lead to non-specific activation of muscles producing motor conflict that may degrade prosthetic gait (Kagerer, Summers & Semjen 2003). Evidence of abnormal EMG patterns during amputee gait (Huang & Ferris 2012) support the idea of motor conflict, and should be further investigated in gait variability studies.

There are two potential limitations of this study to consider. First, amputee participants were higher functioning and may not be representative of the community. Despite this, there were smaller ICE values in amputees with relatively poorer function. Second, there was a lack of homogeneity for indications for amputation across participants. In particular vascular amputations have associated peripheral neuropathies and general deconditioning compared to trauma amputations.

However, of the amputees with negative ICE, only one was a vascular amputee arguing against this confounding factor (see table 7.1). The indication for amputation was controlled for in the ICE and step-time variability regression analysis and was a non-significant factor.

7.6 Conclusion

In conclusion, control of the rectus femoris muscle during normal human gait may depend upon the relative corticomotor excitability between hemispheres; with a predominance of contralateral control. Following amputation, a change in the balance of cortical excitability might affect gait function. In the current study, amputees had smaller ICE values compared to controls, and smaller ICE values were associated with increased step-time variability. This indicates an increase in putative ipsilateral to contralateral excitability may increase step-time variability, which may in turn lead to greater risk of falls in amputees. Future studies should seek to demonstrate causal relationships between measures of cortical neurophysiology, such as ICE, and gait function. This understanding would have the potential to improve amputee clinical practice.

CHAPTER EIGHT: REORGANISATION OF THE PRIMARY MOTOR CORTEX FOLLOWING LOWER-LIMB AMPUTATION

About this chapter:

Earlier chapters in this thesis identified speed normalised spatial-temporal gait variability is associated with falls history and reduced community activity and participation. In chapter seven a neurophysiological biomarker of gait function (ICE) was identified in community amputees. This chapter sought to identify additional neurophysiological biomarkers of gait function in amputees undertaking prosthetic rehabilitation. The research question which is addressed is 'Can TMS measures be used as neurophysiological biomarkers of gait function?' Participants in this study were recruited from the prosthetic rehabilitation facility described in chapter four. Part of this study has been published in *Clinical Neurophysiology*.

8.1 Abstract

Extensive reorganisation occurs at the level of the cortex following limb amputation. This study characterised bilateral corticomotor and intracortical excitability of M1, from pre amputation through to completion of rehabilitation. Thirteen transtibial amputees (10 male, mean age 61.1 (SD 12.4) years) and thirteen age and gender matched healthy control participants were recruited. Single- and paired-pulse transcranial magnetic stimulation assessed corticomotor and intracortical excitability of M1 bilaterally. For all thirteen participants, assessments were conducted at key phases of rehabilitation. For three participants where amputation surgery was elective, an additional pre-amputation neurophysiological assessment was performed. Neurophysiological assessments were performed on impending amputees (n = 3) 10.0 (SD 7.0) days prior to surgery. There were no differences for all neurophysiology measures between impending amputees and controls (all $p > 0.27$) in this small sample. Neurophysiological assessments were performed on amputees (n = 3) 10.0 (SD 4.4) days following amputation. Active motor threshold was higher for M1CON compared to M1IPSI ($p = 0.01$). Following amputation, SICI decreased in both M1CON ($p = 0.01$) and M1IPSI ($p = 0.03$). Long-latency ICI decreased in M1IPSI ($p = 0.02$), but not in M1CON ($p = 0.10$). Intracortical facilitation increased in M1IPSI post amputation, but did not reach significance in these three cases ($p > 0.32$). For amputees across rehabilitation (n = 13), SICI was reduced in M1CON at first walk compared to discharge ($p = 0.003$). For M1IPSI, SICI was reduced at admission ($p = 0.01$) and cast ($p = 0.01$) compared to discharge, while LICI was reduced at admission ($p = 0.05$) and cast ($p = 0.02$) compared to first walk. Importantly, there were significant associations with intracortical excitability and gait function. For

M1CON, there was a negative relationship between SICI at admission ($p = 0.05$) and walk ($p = 0.05$) with step-width variability. For M1IPSI, there was a positive relationship between SICI at discharge with step-length variability ($p = 0.05$). The main findings of this study were that there appears to be bilateral cortical reorganisation associated with lower-limb amputation and prosthetic rehabilitation. There were significant relationships between intracortical measures of both hemispheres and gait function at discharge. Short-latency ICI may be an appropriate biomarker of gait function in this population.

8.2 Introduction

Neurophysiological investigation of animal (Florence & Kaas 1995; Rasmusson 1982) and human (Chen, Cohen & Hallett 2002; Elbert et al. 1994) amputees have established amputation is associated with extensive reorganisation of M1. In humans, reorganisation predominantly occurs at the level of the cortex (Chen et al. 1998a; Fuhr et al. 1992). Research into human cortical reorganisation following amputation has primarily focussed on chronic amputees. Both TMS and functional MRI studies demonstrate expansion of adjacent representations within M1CON (Cohen et al. 1991; Fuhr et al. 1992; Simões et al. 2012). In addition, there is increased corticomotor excitability (Chen et al. 1998a; Cohen et al. 1991; Hall et al. 1990) and activation of a larger percentage of the motoneuron pool (Chen et al. 1998a; Cohen et al. 1991; Fuhr et al. 1992), revealed by TMS. For lower-limb amputees, reorganisation of M1CON is likely mediated by intracortical inhibitory GABAergic interneurons (Chen et al. 1998a), while in upper-limb amputees an increase in activity of facilitatory glutamatergic interneurons has been demonstrated (Schwenkreis et al. 2000). However, it is unknown if M1CON reorganisation in chronic amputees represents long-term plasticity in response to amputation, ongoing motor learning associated with prosthetic mobility, or a combination of these driving influences.

Interestingly, unilateral amputation may also be associated with reorganisation of M1IPSI. Several studies support this proposition. First, lateral displacement of the ipsilateral motor map was reported in chronic lower amputees (Schwenkreis et al. 2003). Second, a positron emission tomography study with chronic upper-limb amputees found increased volume of $GABA_A$ receptors in both M1CON and M1IPSI

(Capaday et al. 2000), indicative of bilateral activity in response to amputation. Since normal cortical control of the lower-limb requires both hemispheres (Luft et al. 2002; Sahyoun et al. 2004), reorganisation of M1IPSI alongside that of M1CON post amputation is unsurprising. Alternatively, increased demand of the non-amputated limb (Schwenkreis et al. 2003), or interhemispheric projections from the reorganising M1CON may facilitate reorganisation of M1IPSI (Werhahn et al. 2002). The neurophysiology of M1IPSI reorganisation following amputation warrants further investigation.

It is possible that patterns of cortical reorganisation following amputation and through prosthetic rehabilitation may be associated with functional outcomes. Examples from stroke literature demonstrate bilateral cortical reorganisation occurs following stroke, and intracortical and corticomotor excitability of both ipsilesional and contralesional M1 have been associated with functional outcomes (Manganotti et al. 2002; Shimizu et al. 2002; Swayne et al. 2008; Trompetto et al. 2000). As intracortical and corticomotor excitability may be modulated bilaterally in the early phase following amputation, it is likely there are functional implications. Reorganisation of inhibitory and facilitatory circuits in the brain may be associated with function as they play a role in regulating output from the motor cortex. Further investigation of function in amputees is warranted given difficulties of prosthetic mobility. Over 50% of amputees report falling in the preceding 12 months (Miller, Speechley & Deathe 2001). For amputees, increased spatial-temporal gait variability is associated with falls and is therefore considered a sensitive measure of gait function (Parker, Hanada & Adderson 2013; Vanicek et al. 2009).

There appears a relative paucity in longitudinal amputee neurophysiology studies to differentiate cortical reorganisation patterns associated with amputation and prosthetic use. Detailed understanding of intracortical and corticomotor excitability of the motor cortex following lower-limb amputation may provide further understanding to basic human neurophysiology associated with amputation, and an opportunity to improve rehabilitation outcomes. Associating patterns of cortical reorganisation with function may guide future studies aiming to provide interventions to improve functional outcomes. Therefore, the purpose of this study was to investigate the longitudinal neurophysiological reorganisation of the motor cortex bilaterally during prosthetic rehabilitation. Amputees were studied prior to amputation surgery through to completion of prosthetic rehabilitation. Neurophysiological assessments were completed at key phases of prosthetic rehabilitation (pre-amputation, rehabilitation admission, prosthetic cast, first walk and discharge (identified in chapter four of this thesis). In addition this study sought to determine association between neurophysiological measures and gait function at discharge. The hypothesis was that lower-limb amputees would experience bilateral reorganisation of M1 which would be mediated by GABAergic inhibition. Furthermore, it was hypothesised that increased corticomotor excitability and reduced intracortical inhibition of $M1_{IPSI}$ would be associated with poor gait function (increased gait variability) at discharge.

8.3 Methods

8.3.1 Participants

Thirteen unilateral transtibial amputees (10 male, mean age 61.1 (SD 12.4) years) admitted for prosthetic rehabilitation at one regional rehabilitation hospital in Adelaide, South Australia were recruited (for a description of the amputee rehabilitation service see chapter four of this thesis). Participants were screened for phantom pain with the pain component of the Prosthetic Evaluation Questionnaire (Boone & Coleman 2006). Participants with phantom pain were excluded. A comparator group of 13 age and gender matched control participants were purposively recruited (mean age 58.9 (SD 9.8) years). Limb dominance was assessed with the Edinburgh Handedness Inventory (Oldfield 1971) and in control participants the non-dominant limb was modelled as the amputated limb. Potential participants with contraindications for TMS, including those with metallic implants, a history of seizures and medications known to alter central nervous system excitability were excluded (Rossi et al. 2009). Ethical approval was provided by the Southern Adelaide Clinical Human Research ethics committee and all participants provided written informed consent in accordance with the Declaration of Helsinki.

8.3.2 Protocol

Participants attended lab sessions to assess brain neurophysiology based on phases of rehabilitation completed. Assessments were conducted at time of admission to rehabilitation, prosthetic casting, first walk, and discharge from rehabilitation. For three participants where amputation surgery was elective, an additional pre-amputation session was performed. During TMS, participants were seated

comfortably with hip and knee joints flexed to 90^0. A seated knee-extension task was used to unilaterally pre-activate the RF muscle prior to each TMS pulse. Consistent muscle activation at 10-15% maximal voluntary contraction was achieved by monitoring visual feedback of raw EMG signal from the RF. Transcranial MS pulses were triggered during muscle contractions using Signal software (v5.09) at a frequency of 0.2Hz.

8.3.3 Electromyography

Surface EMG was recorded from the RF bilaterally using 10mm-diameter Ag/AgCl electrodes (Ambu, Ballerup, Denmark) placed 2cm apart over the muscle bellies. The distal electrode positioned approximately 12cm proximal to the superior pole of the patella. A 20mm-diameter reference Ag/AgCl electrode was placed over the patella (3M Health Care, Canada). Prior to affixing the electrodes, hair was removed, and the top layer of skin was lightly abraded for optimal contact. Electromyography signals were sampled at 2000Hz (CED 1401; UK), amplified (CED 1902; UK), band-pass filtered (20-1000Hz) and stored for offline analysis (Signal v5.09).

8.3.4 Transcranial magnetic stimulation

Single-pulse TMS was delivered using a Magstim 200 stimulator, and paired-pulse TMS was delivered using two stimulators connected to a BiStim^2 unit (Magstim Company, Dyfed, UK). A flat 70mm wing diameter, figure eight coil was held tangentially over the scalp with the handle pointing 30° posterior-medially in the transverse plane. This coil orientation was determined from extensive piloting. As a guide, the coil was initially positioned 1cm posterior, 1.5cm lateral to the vertex (Madhavan, Rogers & Stinear 2010). The ‘hotspot’ for evoking maximal responses

in the contralateral active RF was then determined for each M1 by systematically moving the coil over a 1cm grid from this location and marked on the scalp. Active MT was determined separately for each M1 as the minimum stimulus intensity eliciting a 100μV MEP in five of ten stimuli in the contralateral RF (Rossini et al. 1994). For single-pulse TMS, 16 MEPs were evoked at 120%AMT from each M1 in turn. For paired-pulse TMS, 16 non-conditioned and 16 conditioned MEPs were evoked in randomised order. Short-latency ICI, ICF and LICI were assessed. For all paired-pulse measures, the test stimulus was set to the stimulus intensity corresponding to a half maximum MEP (50%MEP$_{MAX}$), ensuring the test MEP was evoked from the linear portion of the stimulus response curve for each individual (Devanne, Lavoie & Capaday 1997). This method allows for MEP facilitation or suppression during paired-pulse measures while avoiding ceiling or floor effects, and any effect of pre-to-post amputation changes in corticomotor excitability (Garry & Thomson 2009). Short-latency ICI was assessed using three conditioning stimulus intensities (70%AMT, 80%AMT and 90%AMT) with an inter-stimulus-interval of 2ms, generating a SICI recruitment-curve (Peurala et al. 2008; Talelli et al. 2011). For each individual, the conditioning stimulus which evoked the greatest degree of SICI at their first assessment was compared across sessions. Intracortical facilitation was assessed using a conditioning stimulus intensity of 80% and two inter-stimulus-intervals of 10ms and 15ms (Talelli et al. 2011). The inter-stimulus interval which evoked greatest ICF at the first assessment was compared across sessions. Long-latency ICI was assessed using a suprathreshold conditioning stimulus (50%MEPmax) delivered 100ms before the test stimulus (McDonnell, Orekhov & Ziemann 2006).

For both single- and paired-pulse TMS, MEPs where pre-stimulus rmsEMG were two standard deviations above or below the mean were removed prior to averaging (range 0-3) to ensure consistency of MEP responses. From the retained traces MEPs were measured peak-to-peak and paired-pulse measures were expressed as (conditioned MEP / non-conditioned MEP) x 100.

8.3.5 Spatial-temporal gait variability

Spatial-temporal gait was assessed using an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA). Embedded pressure sensors to capture individual footfall data over an active area 4.9m x 0.6m. Participants completed 10 consecutive passes over the GAITRite at their self-selected comfortable walking speed. Data were collected at 120Hz and analysed using GAITRite software (version 4.5.5). The CV, calculated as SD divided by the mean, was used to assess variability of spatial-temporal parameters. Step-time, step-length and step-width variability were reported due to previous use with amputees and older adults (Brach et al. 2008; Parker, Hanada & Adderson 2013; Vanicek et al. 2009; Verghese et al. 2007). Step parameters were selected in preference to stride parameters for their improved clinometric properties (Moe-Nilssen et al. 2010). Primary gait variability outcome measures are speed dependant parameters and greater variability can occur in raw data with variations in walking speed between trials (Beauchet et al. 2009). Individual gait trials were therefore normalised to walking speed prior to calculation of CV in accordance with similar previous studies (Helbostad & Moe-Nilssen 2003; Hof 1996; Van Iersel, Olde Rikkert & Borm 2007).

8.3.6 Data analysis

The normality of data were checked with a Shapiro-Wilk normality test. Motor EP amplitude and ICF in M1CON and M1IPSI were log transformed to achieve normality. Significance level was set at $p \leq 0.05$. Post-hoc tests explored significant effects and were corrected for multiple comparisons using a modified Bonferroni correction (Rom 1990). SPSS software was used for all statistical analyses (IBM corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0).

8.3.6.1 Demographics

Age was compared between the three impending amputees and controls with an independent t-test. Similarly, age of 13 amputees completing rehabilitation and controls was assessed with an independent t-test.

8.3.6.2 Neurophysiological assessments pre and post amputation

Impending amputees and controls

Neurophysiological measures AMT, MEP amplitude (120%AMT), SICI, ICF and LICI were compared between impending amputees and controls with separate one-way ANOVAs. The four independent variables were neurophysiological measures from M1CON and M1IPSI for both impending amputees and controls. Background rmsEMG when assessing single-pulse MEPs at 120%AMT were compared between impending amputees and controls for both hemispheres with a one-way ANOVA. Background rmsEMG for paired-pulse measures (SICI, ICF and LICI) was compared for conditioned and non-conditioned MEPs evoked from M1CON and M1IPSI between impending amputees and controls with separate one-way ANOVAs.

Pre and post amputation

Neurophysiological measures AMT, MEP amplitude (120%AMT), SICI, ICF and LICI were compared pre and post amputation with separate 2 time (pre amputation, post amputation) x 2 hemisphere ($M1_{CON}$, $M1_{IPSI}$) repeated measures ANOVA (rmANOVA). Background rmsEMG when assessing single-pulse MEPs at 120%AMT was compared using the same rmANOVA. Background rmsEMG for paired-pulse measures (SICI, ICF and LICI) was compared pre and post amputation with separate 2 time (pre amputation, post amputation) x 2 hemisphere ($M1_{CON}$, $M1_{IPSI}$) x 2 conditioned (conditioned, non-conditioned MEP) rmANOVA.

8.3.6.3 Neurophysiological assessments through prosthetic rehabilitation

Amputees through rehabilitation

For amputees, neurophysiological measures AMT, MEP amplitude (120%AMT), SICI, ICF and LICI were individually assessed with separate 2 hemisphere ($M1_{CON}$, $M1_{IPSI}$) x 4 time (admission, cast, walk, discharge) rmANOVA. Background rmsEMG when assessing single-pulse MEPs at 120%AMT was compared using the same rmANOVA. Background rmsEMG for paired-pulse measures (SICI, ICF and LICI) was compared with separate 2 hemisphere ($M1_{CON}$, $M1_{IPSI}$) x 4 time (admission, cast, walk, discharge) x 2 conditioned (conditioned, non-conditioned MEP) rmANOVA.

Amputees and controls at discharge

Neurophysiological measures AMT, MEP amplitude (120%AMT), SICI, ICF and LICI for each M1 were compared between amputees at discharge and controls with separate one-way ANOVAs. The four independent variables were

neurophysiological measures from M1CON and M1IPSI for both impending amputees and controls. Background rmsEMG when assessing single-pulse MEPs at 120%AMT were compared between impending amputees and controls for both hemispheres with a one-way ANOVA. Background rmsEMG for paired-pulse measures (SICI, ICF and LICI) was compared for conditioned and non-conditioned MEPs evoked from M1CON and M1IPSI between impending amputees and controls with separate one-way ANOVAs.

8.3.6.4 Association with gait function

Step-time, step-length and step-width variability were compared between amputees and controls with separate independent t-tests. The relationships between gait function (step-time, step-length and step-width variability) and neurophysiology measures (AMT, MEP amplitude, SICI, LICI, ICF) were assessed for each test session with linear regression analysis. Linear regression models were controlled for age and stump length as these factors can affect gait function (Callisaya et al. 2010; Gonzalez, Corcoran & Reyes 1974; Kang & Dingwell 2008).

8.4 Results

8.4.1 Demographics

There were no differences in age between impending amputees (n = 3) (49.3 (SD 5.1)) or controls (50.0 (SD 5.3)) (p = 0.88). For the thirteen amputees completing rehabilitation, there were no differences in age between amputees (61.1 (SD 12.4)) or controls (58.9 (SD 9.8)) (p = 0.49).

8.4.2 Neurophysiological assessment of impending amputees and controls

Impending amputees and controls

Three amputees were tested 10.0 (SD 7.0) days pre-amputation. There were no differences between impending amputees and controls for all neurophysiology measures (all $p > 0.48$). There was no difference in background rmsEMG between impending amputees and controls for all measures (all $p > 0.11$).

Pre and post amputation

Neurophysiological assessments were performed on amputees 10.0 (SD 4.4) days following amputation. A summary of neurophysiology measures is provided in table 8.1. For AMT there was a main effect of hemisphere ($F_{(1,2)} = 50.4$, $p = 0.01$) but no other main effects or interactions ($p > 0.18$). Post-hoc analysis revealed AMT was higher in M1CON than M1IPSI ($t_{(2)} = 10.0$, $p = 0.01$) following amputation. For single-pulse MEP amplitude there were no main effects or interactions ($p > 0.37$). For SICI there was a main effect of time ($F_{(1,2)} = 26.2$, $p = 0.02$). The main effect of hemisphere ($p = 0.25$) and time by hemisphere interaction ($p = 0.08$) did not reach significance. Post-hoc analysis revealed SICI in M1CON ($t_{(2)} = 8.06$, $p = 0.01$) and SICI in M1IPSI ($t_{(2)} = 3.77$, $p = 0.03$) decreased following amputation. For ICF there were no main effects or interactions ($p > 0.32$). For LICI there was a main effect of time ($F_{(1,2)} = 11.1$, $p = 0.04$) and hemisphere ($F_{(1,2)} = 50.9$, $p = 0.01$) but no interaction ($p = 0.37$). Post-hoc analysis revealed LICI in M1IPSI decreased following amputation ($t_{(2)} = 4.28$, $p = 0.02$), but not in M1CON ($p = 0.10$). There was comparatively less LICI in M1CON following amputation ($t_{(2)} = 3.87$, $p = 0.03$), but not pre amputation ($p = 0.15$). There was no difference in background rmsEMG

between pre and post amputation for all measures (all $p > 0.12$) (see table 8.2). Test MEP amplitude is reported in table 8.3.

Table 8.1: Pre and post amputation neurophysiological measures.

	Control (n = 3)	Amputee Pre Amputation (n = 3)	Amputee Post Amputation (n = 3)
AMT $M1_{CON}$ (%MSO)	46.0 (12.5)	57.3 (14.8)	67.0 (18.5)^
AMT $M1_{IPSI}$ (%MSO)	42.7 (11.8)	51.3 (18.0)	49.3 (17.6)^
MEP Amplitude $M1_{CON}$ (mV)	0.36 (0.3)	0.35 (0.2)	0.39 (0.3)
MEP Amplitude $M1_{IPSI}$ (mV)	0.33 (0.1)	0.22 (0.1)	0.35 (0.2)
SICI $M1_{CON}$ (% test MEP)	85.1 (19.6)	72.4 (15.9)*	82.4 (13.8)*
SICI $M1_{IPSI}$ (% test MEP)	86.5 (7.1)	74.2 (6.9)*	101.3 (8.1)*
ICF $M1_{CON}$ (% test MEP)	114.7 (13.7)	117.3 (12.5)	112.8 (18.4)
ICF $M1_{IPSI}$ (% test MEP)	113.8 (3.5)	104.9 (5.3)	117.2 (25.6)
LICI $M1_{CON}$ (% test MEP)	56.5 (23.0)	82.5 (9.8)	95.3 (21.0) ^
LICI $M1_{IPSI}$ (% test MEP)	69.2 (34.4)	75.4 (18.4)*	85.3 (16.5)* ^

^ Significant differences between hemispheres following amputation for AMT and LICI

* Significant differences pre and post amputation for SICI evoked in $M1_{CON}$ and $M1_{IPSI}$, and LICI evoked in $M1_{IPSI}$

AMT, active motor threshold; MEP, motor evoked potential; SICI, short-latency intracortical inhibition; ICF, intracortical facilitation; LICI, long-latency intracortical inhibition; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex contralateral to the non-amputated limb.

Table 8.2: rmsEMG (mV) pre and post amputation.

	Control (n = 3)		Amputee Pre Amputation (n = 3)		Amputee Post Amputation (n = 3)	
	C	NC	C	NC	C	NC
MEP $M1_{CON}$		0.04 (0.02)		0.04 (0.01)		0.02 (0.01)
MEP $M1_{IPSI}$		0.04 (0.02)		0.04 (0.01)		0.05 (0.04)
SICI $M1_{CON}$	0.03 (0.01)	0.03 (0.01)	0.04 (0.00)	0.05 (0.00)	0.03 (0.02)	0.03 (0.02)
SICI $M1_{IPSI}$	0.03 (0.01)	0.03 (0.01)	0.05 (0.02)	0.06 (0.02)	0.06 (0.05)	0.06 (0.05)
ICF $M1_{CON}$	0.03 (0.01)	0.03 (0.01)	0.04 (0.00)	0.05 (0.00)	0.03 (0.01)	0.03 (0.01)
ICF $M1_{IPSI}$	0.03 (0.00)	0.02 (0.01)	0.05 (0.03)	0.05 (0.03)	0.05 (0.03)	0.05 (0.03)
LICI $M1_{CON}$	0.03 (0.01)	0.03 (0.01)	0.05 (0.01)	0.05 (0.01)	0.03 (0.01)	0.03 (0.01)
LICI $M1_{IPSI}$	0.02 (0.01)	0.02 (0.01)	0.05 (0.04)	0.06 (0.04)	0.04 (0.02)	0.04 (0.02)

C, conditioned MEPs; NC, non-conditioned MEPs; MEP, motor evoked potential; SICI, short-latency intracortical inhibition; ICF, intracortical facilitation; LICI, long-latency intracortical inhibition; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex contralateral to the non-amputated limb.

Table 8.3: Paired-pulse test MEP size (mV) pre and post amputation.

	Control (n = 3)	Amputee Pre Amputation (n = 3)	Amputee Post Amputation (n = 3)
SICI $M1_{CON}$	0.41 (0.27)	1.03 (1.03)	0.53 (0.67)
SICI $M1_{IPSI}$	0.45 (0.13)	1.41 (1.69)	0.76 (0.89)
ICF $M1_{CON}$	0.38 (0.21)	0.94 (0.93)	0.33 (0.39)
ICF $M1_{IPSI}$	0.35 (0.13)	0.92 (0.84)	0.64 (0.66)
LICI $M1_{CON}$	0.39 (0.28)	0.83 (0.74)	0.39 (0.46)
LICI $M1_{IPSI}$	0.39 (0.22)	1.21 (1.43)	0.42 (0.38)

SICI, short-latency intracortical inhibition; ICF, intracortical facilitation; LICI, long-latency intracortical inhibition; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex contralateral to the non-amputated limb.

8.4.3 Neurophysiological assessments through prosthetic rehabilitation

Amputees through rehabilitation

For amputees across rehabilitation, there were no main effects or interactions for AMT ($p > 0.36$), or MEP amplitude ($p > 0.40$). There was significant modulation of SICI for $M1_{CON}$ ($F_{(3,36)} = 2.47$, $p = 0.05$). Post-hoc analysis found that compared to discharge, there was reduced inhibition at walk ($t_{(12)} = 3.66$, $p = 0.003$). There was significant modulation of SICI for $M1_{IPSI}$ ($F_{(3,36)} = 3.42$, $p = 0.03$). Post-hoc analysis found that compared to discharge, there was reduced inhibition at admission ($t_{(12)} = 3.36$, $p = 0.006$) and cast ($t_{(12)} = 3.38$, $p = 0.005$) (see figure 8.1). There was no

modulation of ICF ($p > 0.25$) (see figure 8.2). There was no modulation of LICI for $M1_{CON}$ ($p = 0.52$). There was significant modulation of LICI for $M1_{IPSI}$ ($F_{(3,36)} = 2.19$, $p = 0.05$). Post-hoc analysis found that compared to walk, there was a reduced inhibition at admission ($t_{(12)} = 2.14$, $p = 0.05$) and cast ($t_{(12)} = 2.92$, $p = 0.02$) (see figure 8.3).

For amputees, analysis of background rmsEMG found a significant main effect of hemisphere ($p = 0.01$) for MEP amplitude. There were no other main effects or interactions ($p > 0.15$). For SICI, there was a significant main effect of hemisphere ($p = 0.01$). There were no other main effects or interactions ($p > 0.17$). For ICF, there was a significant main effect of hemisphere ($p = 0.01$). There were no other main effects or interactions ($p > 0.16$). For LICI, there was a significant main effect of hemisphere ($p = 0.01$). There were no other main effects or interactions ($p > 0.07$). Main effects of hemisphere were expected as reduced muscle activity would be required to pre-activate the RF of the amputated limb. This finding does not confound interpretation of results as this study does not compare results between hemispheres.

Amputees and controls at discharge

There were no differences for neurophysiological measures between controls and amputees at discharge (all $p > 0.18$). Analysis of background rmsEMG found no significant differences for all neurophysiological measures (all $p > 0.09$). Background rmsEMG and test MEP amplitude are provided in tables 8.4 and 8.5.

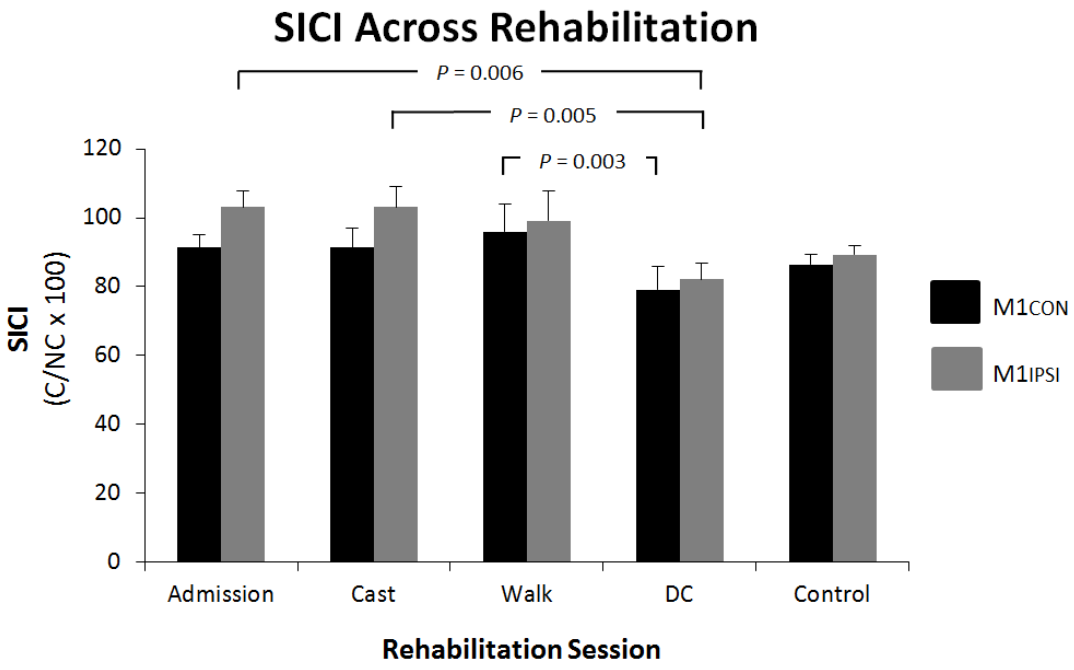

Figure 8.1: Modulation of SICI across rehabilitation for M1CON and M1IPSI. Admission, rehabilitation admission; Cast, prosthetic cast; Walk, first walk; DC, discharge; SICI, short-latency intracortical inhibition; M1CON, primary motor cortex contralateral to the amputated limb; M1IPSI, primary motor cortex ipsilateral to the amputated limb.

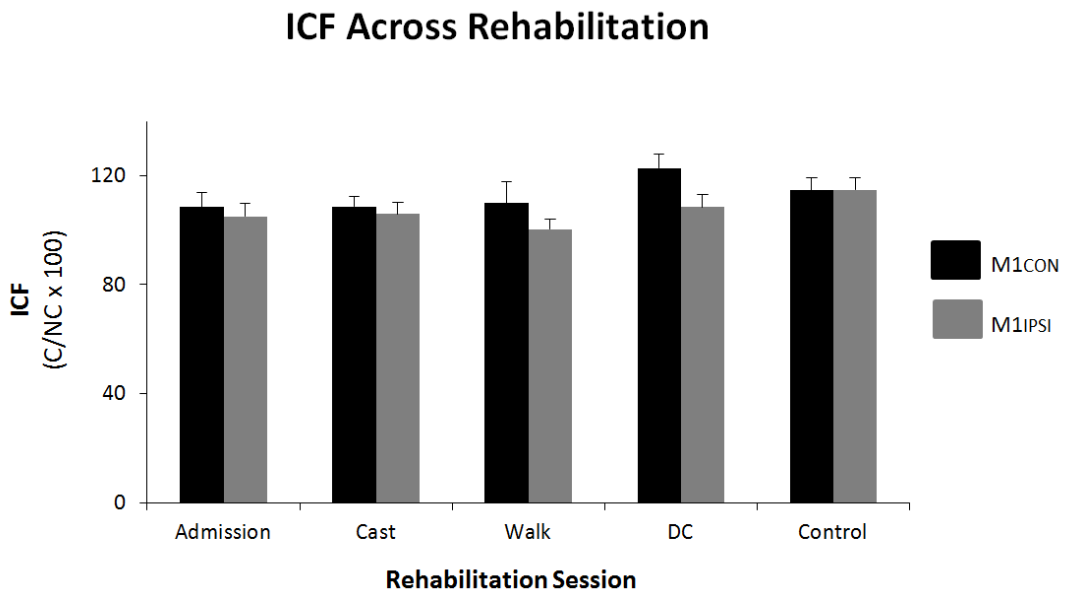

Figure 8.2: Modulation of ICF across rehabilitation for M1CON and M1IPSI. Admission, rehabilitation admission; Cast, prosthetic cast; Walk, first walk; DC, discharge; ICF, intracortical facilitation; M1CON, primary motor cortex contralateral to the amputated limb; M1IPSI, primary motor cortex ipsilateral to the amputated limb.

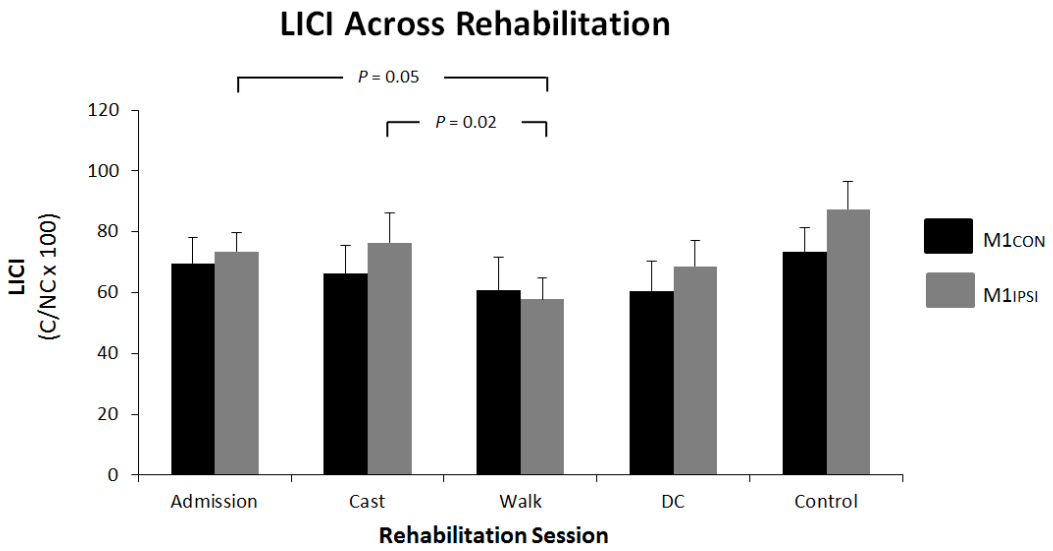

Figure 8.3: Modulation of LICI across rehabilitation for M1CON and M1IPSI. Admission, rehabilitation admission; Cast, prosthetic cast; Walk, first walk; DC, discharge; LICI, long-latency intracortical inhibition; M1CON, primary motor cortex contralateral to the amputated limb; M1IPSI, primary motor cortex ipsilateral to the amputated limb.

Table 8.4: rmsEMG (mV) of amputees across rehabilitation and control subjects.

	Control (n=13)		Amputee Admission (n=13)		Amputee Cast (n=13)		Amputee Walk (n=13)		Amputee DC (n=13)	
	C	NC	C	NC	C	NC	C	NC	C	NC
MEP $M1_{CON}$		0.04 (0.02)		0.04 (0.01)		0.03 (0.02)		0.02 (0.01)		0.02 (0.01)
MEP $M1_{IPSI}$		0.05 (0.03)		0.05 (0.03)		0.05 (0.06)		0.04 (0.03)		0.03 (0.02)
SICI $M1_{CON}$	0.05 (0.02)	0.05 (0.02)	0.03 (0.03)	0.03 (0.04)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.01)	0.03 (0.01)
SICI $M1_{IPSI}$	0.06 (0.04)	0.06 (0.04)	0.06 (0.04)	0.06 (0.05)	0.05 (0.06)	0.05 (0.06)	0.05 (0.03)	0.05 (0.03)	0.03 (0.02)	0.03 (0.02)
ICF $M1_{CON}$	0.05 (0.02)	0.05 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.02 (0.01)	0.03 (0.02)	0.02 (0.01)	0.02 (0.01)
ICF $M1_{IPSI}$	0.05 (0.05)	0.05 (0.04)	0.05 (0.03)	0.05 (0.03)	0.05 (0.05)	0.05 (0.05)	0.04 (0.02)	0.04 (0.02)	0.03 (0.02)	0.03 (0.02)
LICI $M1_{CON}$	0.05 (0.03)	0.05 (0.03)	0.05 (0.04)	0.04 (0.04)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.02 (0.01)	0.02 (0.01)
LICI $M1_{IPSI}$	0.06 (0.04)	0.06(0.04)	0.07 (0.04)	0.07 (0.04)	0.05 (0.06)	0.05 (0.06)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)

C, conditioned MEPs; NC, non-conditioned MEPs; MEP, motor evoked potential; SICI, short-latency intracortical inhibition; ICF, intracortical facilitation; LICI, long-latency intracortical inhibition; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex contralateral to the non-amputated limb; Admission, rehabilitation admission; Cast, prosthetic cast; Walk, first walk; DC, discharge.

Table 8.5: Paired-pulse test MEP size (mV) of amputees averaged across rehabilitation and control subjects.

	Amputee (n=13)	Control (n=13)
SICI M1CON	0.43 (0.42)	0.73 (0.33)
SICI M1IPSI	0.52 (0.35)	0.79 (0.83)
ICF M1CON	0.37 (0.29)	0.66 (0.32)
ICF M1IPSI	0.54 (0.41)	0.72 (0.79)
LICI M1CON	0.40 (0.33)	0.67 (0.32)
LICI M1IPSI	0.55 (0.41)	0.75 (0.69)

SICI, short-latency intracortical inhibition; ICF, intracortical facilitation; LICI, long-latency intracortical inhibition; M1CON, primary motor cortex contralateral to the amputated limb; M1IPSI, primary motor cortex contralateral to the non-amputated limb.

8.4.4 Association with gait function

Linear regression models controlling for age and stump length demonstrated a negative relationship between SICI assessed in M1CON at admission and step-width variability ($R^2 = 0.45$, $p = 0.045$) (see figure 8.4). No other independent variables controlled for were significant ($p > 0.10$). There was a negative relationship between SICI assessed in M1CON at walk and step-width variability ($R^2 = 0.46$, $p = 0.050$) (see figure 8.5). No other independent variables controlled for were significant ($p > 0.07$). There was a positive relationship between SICI assessed in M1IPSI at discharge and step-length variability ($R^2 = 0.46$, $p = 0.047$) (see figure 8.6). No other

independent variables controlled for were significant ($p > 0.08$). There were no other associations between neurophysiological measures and gait variability (all $p > 0.11$).

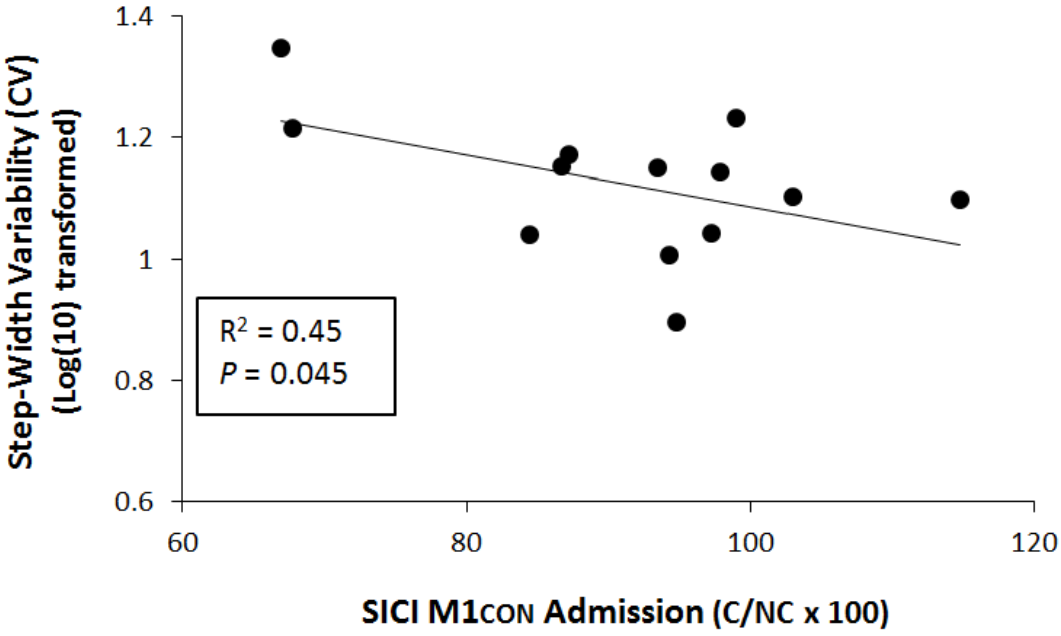

Figure 8.4: Linear regression analysis between step-width variability (log transformed) and SICI in M1CON at admisssion.

There was a significant negative relationship indicating disinhibition was associated with smaller step-width variability.

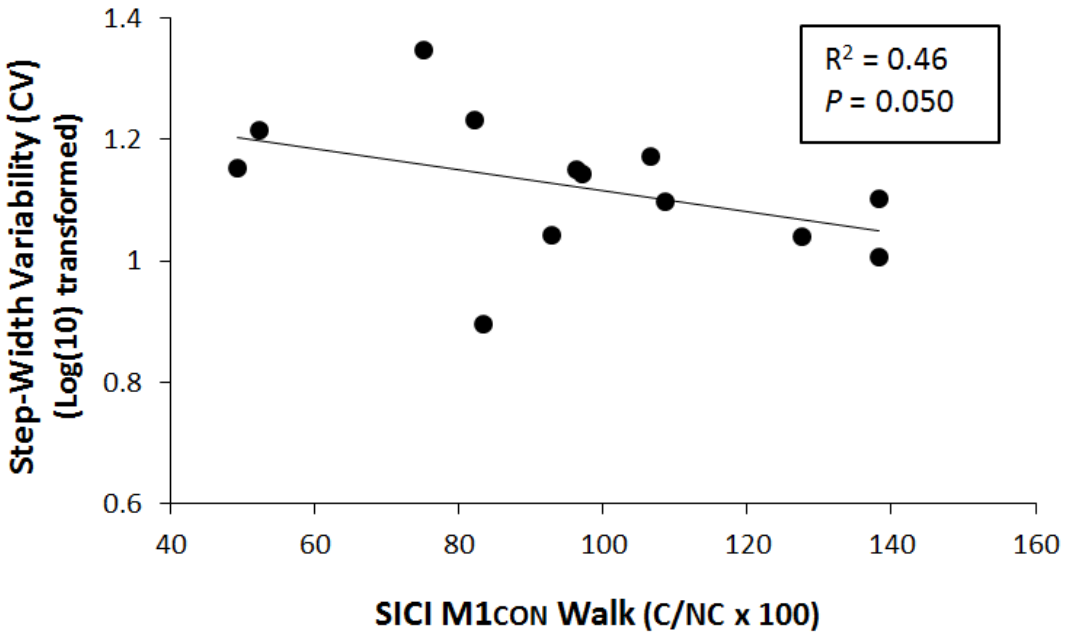

Figure 8.5: Linear regression analysis between step-width variability (log transformed) and SICI in M1CON at walk.

There was a significant negative relationship indicating disinhibition was associated with smaller step-width variability.

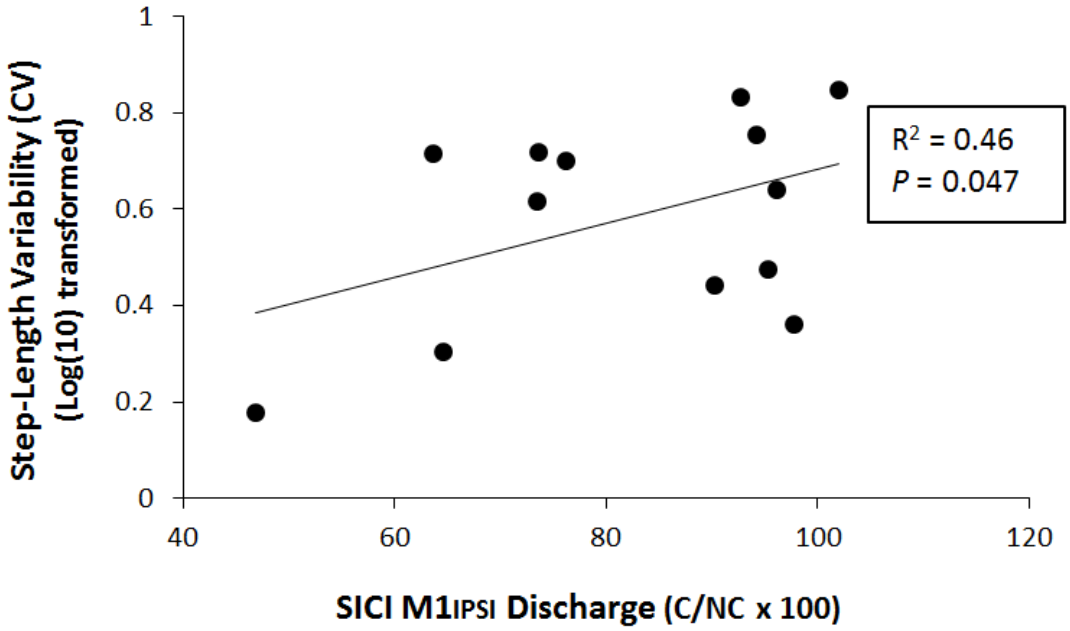

Figure 8.6: Linear regression analysis between step-length variability (log transformed) and SICI in M1IPSI at discharge.

There was a significant positive relationship indicating disinhibition was associated with greater step-length variability.

8.5 Discussion

The main findings of this study were that there was bilateral modulation of the primary motor cortices as a result of amputation and prosthetic rehabilitation. Active MT was higher in M1CON than M1IPSI post amputation. For M1CON, there was modulation of inhibitory GABAergic neurons assessed as SICI. For M1IPSI, there was modulation of inhibitory GABAergic neurons assessed as SICI and LICI. Disinhibition of M1CON at admission and walk was associated with better gait function, while disinhibition of M1IPSI at discharge was associated with poorer gait function.

This is the first study to directly demonstrate cortical reorganisation in lower-limb amputees by analysing neurophysiological measures pre and post amputation surgery. A previous single upper-limb case report assessed cortical reorganisation five weeks post traumatic transradial amputation and reported expansion of the motor map (Pascual-Leone et al. 1996). In the current study, post amputation measures were taken much closer to time of surgery, prior to beginning rehabilitation and this study used paired-pulse TMS measures to understand mechanisms associated with cortical reorganisation. Phantom pain was not experienced by the amputees in this study, and therefore was not a factor in the pattern of reorganisation reported here. The most noteworthy effect of amputation on the cortex was disinhibition in $M1_{CON}$, assessed as SICI. During SICI the initial conditioning stimulus is thought to produce an inhibitory post-synaptic potential in corticospinal neurons through activation of low-threshold inhibitory interneurons. The result is inhibition of the action potential generated by the second suprathreshold test stimulus (Ilić et al. 2002; Kujirai et al. 1993). Short ICI is considered to reflect activity of inhibitory GABAergic interneurons (figure 8.7). This view is supported by pharmacology studies which indicate SICI reflects $GABA_A$ receptor mediated inhibition as administration of $GABA_A$ receptor agonists lorazepam (Di Lazzaro et al. 2000; Di Lazzaro et al. 2005a; Di Lazzaro et al. 2005b; Ziemann et al. 1996a) and diazepam (Di Lazzaro et al. 2005b; Ilić et al. 2002) increase SICI. GABAergic neurons constitute approximately 25-30% of the cortical neuronal population (Jones 1993) and are crucial to the maintenance of cortical representation (Jacobs & Donoghue 1991; Matsumura, Sawaguchi & Kubota 1992). Reduction in the activity of inhibitory GABAergic interneurons may facilitate strengthening of synaptic efficiency, or unmask latent connections, to drive reorganisation of muscle representations within

M1 (Jacobs & Donoghue 1991). Modulation of $GABA_A$ receptors has been reported for chronic lower-limb amputees in M1CON (Chen et al. 1998a). These amputees were many years since their amputation, potentially indicating ongoing GABAergic-mediated cortical reorganisation. In the current study, there was a reduction of $GABA_A$ inhibition pre-to-post amputation in M1 bilaterally, indicating a release of SICI is a probable mechanism underlying cortical reorganisation following amputation.

There was higher AMT in M1CON compared to M1IPSI following amputation, which was not apparent pre amputation. Motor threshold is thought to reflect intrinsic neuronal membrane excitability and is dependent on ion channel conductivity (Ziemann et al. 1996b). Higher AMT in the early stages following lower-limb amputation conflicts with previous research that found rest motor threshold in chronic amputees was reduced (Chen et al. 1998a). However, a possible explanation for the difference between their results and those of the current study is that these findings suggest modulation of motor threshold occurs over time. It is hypothesised that higher thresholds immediately after amputation may reduce over time with increased prosthetic use. This requires further investigation.

Modulation of inhibitory GABAergic neurons in the contralateral M1 continued across rehabilitation. Disinhibition was observed at time of walking, but was restored at discharge. This may suggest disinhibition assessed at the walking phase is potentially a use-dependent response as this is the first occasion amputees have begun to use their prosthetic limb on the amputated side. Reduction of GABAergic inhibitory interneurons has previously been associated with motor learning (Perez et

al. 2004; Stagg, Bachtiar & Johansen-Berg 2011). The walking phase of rehabilitation can take place almost two months post amputation surgery (see chapter four of this thesis). This indicates modulation of inhibitory GABAergic neurons is unlikely to be related to the limb amputation itself. This finding may represent a plasticity response driven by motor learning associated with prosthetic rehabilitation. It is acknowledged that plasticity of the cortex is an ongoing process, but it is suggested that phases of prosthetic rehabilitation may be associated with an increase or decrease of this plasticity response. It is likely modulation of inhibitory GABAergic interneurons in M1 are associated with activities performed in rehabilitation.

Interestingly cortical reorganisation following amputation was not limited to $M1_{CON}$. There was reduced SICI and LICI in $M1_{IPSI}$ following amputation. Short-latency ICI and LICI represent distinct inhibitory systems within the motor cortex (Sanger, Garg & Chen 2001). Long-latency ICI is evoked by two suprathreshold pulses separated by long inter-stimulus intervals (Di Lazzaro et al. 2002; Nakamura et al. 1997; Valls-Solé et al. 1992). Long-latency ICI is attributed to slow inhibitory post-synaptic potentials mediated by the $GABA_B$ receptor (McDonnell, Orekhov & Ziemann 2006; Sanger, Garg & Chen 2001; Werhahn et al. 1999). Cortical interneurons responsible for LICI directly inhibit corticospinal output via post-synaptic $GABA_B$ receptors (see LICI circuit 1, figure 8.7) *and* pre-synaptic $GABA_B$ receptors on inhibitory interneurons responsible for SICI (see LICI circuit 2, figure 8.7). Accordingly, activities in inhibitory neural circuits are not independent of each other and SICI is reduced in the presence of LICI (Sanger, Garg & Chen 2001). The modulation of SICI by LICI is hypothesised to occur through pre-synaptic $GABA_B$ receptors that

provide a degree of auto-inhibition. Evidence from the rat neocortex indicates physiology of pre- and post-synaptic $GABA_B$ receptors differ. Barium ions, which depress $GABA_B$ receptor mediated potassium conductance, and phaclofen, a $GABA_B$ receptor antagonist had no effect on pre-synaptic auto-inhibition of the inhibitory interneuron, but reduced inhibitory post-synaptic potentials (Deisz, Billard & Zieglgänsberger 1993; Deisz, Billard & Zieglgänsberger 1997). These results indicate distinct pharmacological differences exist between pre-synaptic and post-synaptic $GABA_B$ receptors. In the current study, both LICI and SICI were decreased in $M1_{IPSI}$ post amputation; therefore it is unlikely decreased LICI was associated with reduced auto-inhibition of the inhibitory interneuron. It is more probable that LICI was attenuated in this study because of reduced post-synaptic $GABA_B$ receptor activity, although this suggestion is not certain. Triple-pulse TMS techniques could be used to investigate potential interactions in inhibitory neural circuits in future studies (Ni et al. 2011). This may elucidate mechanisms of SICI, LICI and their interaction in $M1_{IPSI}$ post amputation.

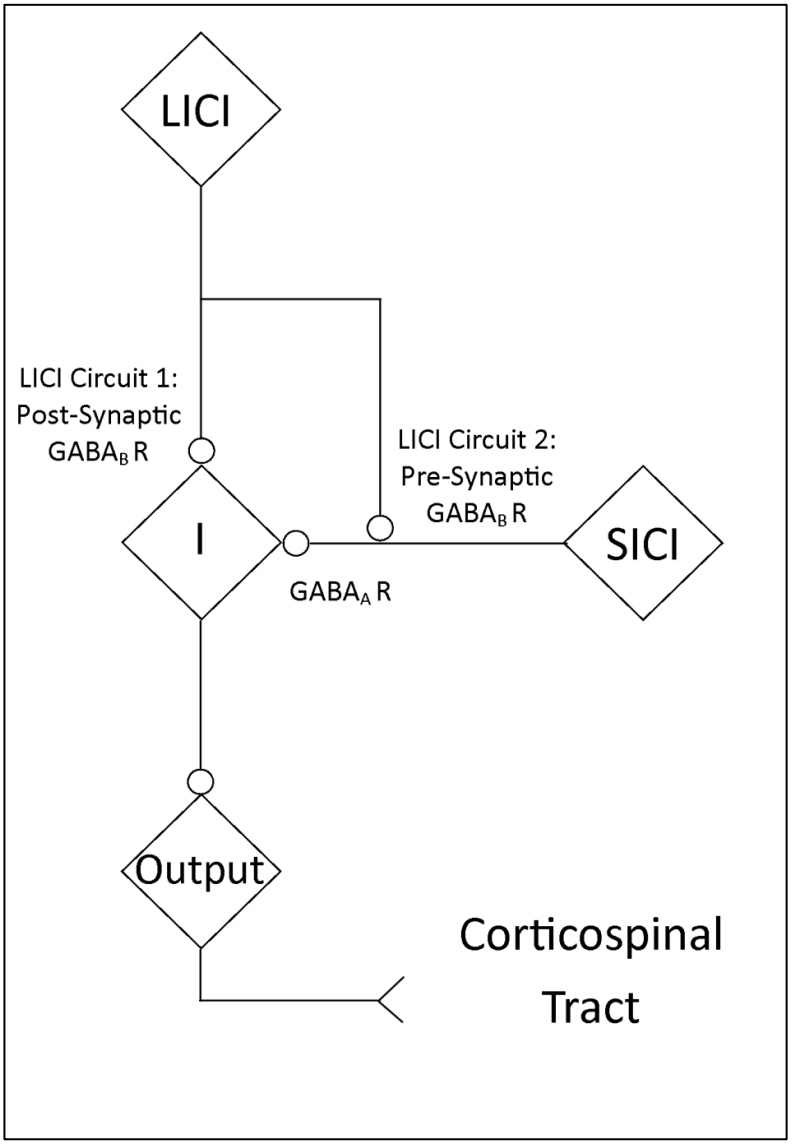

Figure 8.7: Interaction between intracortical inhibitory circuits within the motor cortex of one hemisphere.

Both SICI and LICI inhibit neurons generating I-waves. Cortical interneurons responsible for LICI directly inhibit corticospinal output via post-synaptic $GABA_B$ receptors (LICI circuit 1) *and* pre-synaptic $GABA_B$ receptors on inhibitory interneurons responsible for SICI (LICI circuit 2).

SICI, short-latency intracortical inhibition; LICI, long-latency intracortical inhibition; I, inter-neurons in the outer layers of the cortex; Output, descending corticospinal tract neurons

Reduced excitability of M1IPSI inhibitory intracortical circuits following amputation confirm previous suggestions of bilateral cortical reorganisation post unilateral amputation (Capaday et al. 2000; Schwenkreis et al. 2003). Bilateral modulation post amputation might not be surprising given there is bilateral M1 control over the lower-limb in healthy adults (Luft et al. 2002; Sahyoun et al. 2004). Functional MRI indicates bilateral activation of M1 for motor control of the lower-limb is also important in lower-limb amputees (Cruz et al. 2003b; Simões et al. 2012). The mechanism is unclear, however, upper-limb models suggest M1IPSI may contribute to motor output through ipsilateral descending and interhemispheric projections (Bradnam, Stinear & Byblow 2013; Gerloff et al. 1998; Perez & Cohen 2008). It has been shown there is up-regulation of ipsilateral projections to motoneurons innervating residual muscles of the amputated limb in chronic amputees (see chapter seven of this thesis). Therefore up-regulation of ipsilateral projections is a likely explanation for reduced excitability of M1IPSI inhibitory intracortical circuits observed in this study following amputation. A second possibility is that reorganisation of M1IPSI may represent a use-dependent cortical response as the sound limb may compensate for deficits associated with using the amputated limb. This is a plausible explanation considering amputees undergo mobility training with a prosthetic limb. Loss of plantar flexors on the amputated limb would require compensation by the sound limb to achieve propulsion during gait (Silverman et al. 2008). However, reorganisation of M1IPSI occurred immediately after amputation, prior to rehabilitation, arguing against this explanation during the acute stage. It is also possible that modulation of interhemispheric inhibition (IHI) from the reorganising M1CON might drive reorganisation of M1IPSI. In the upper-limb,

interhemispheric pathways contribute to bimanual coordination, recruiting inhibitory circuits for unimanual movements (Carson 2005). One study demonstrated a reduction in IHI from M1CON to M1IPSI in the upper-limb following limb transient deafferentation (Werhahn et al. 2002). However, IHI was assessed distal to the level of deafferentation making results difficult to translate to amputee studies which can only assess cortical representations proximal to the amputation. It was previously demonstrated that the ipsilateral silent period, an indirect measure of IHI (Chen, Yung & Li 2003; Trompetto et al. 2004), is similar for lower-limb amputees and control subjects (see chapter seven of this thesis). This finding indicates IHI may not be associated with M1IPSI reorganisation following lower-limb amputation. The most parsimonious explanation for M1IPSI reorganisation after amputation is that both cortices control the ipsilateral lower-limb and therefore, cortical reorganisation following unilateral amputation is bilateral.

It was demonstrated that ICF was not altered by amputation or prosthetic rehabilitation in this cohort of lower-limb amputees. However, from observation of the data it appears ICF in M1IPSI was reduced prior to amputation and normalised following amputation (see table 8.1). The actual effect of amputation and prosthetic rehabilitation on ICF is difficult to discern in this sample. A previous study in the upper-limb indicated greater ICF within M1CON compared to M1IPSI (Schwenkreis et al. 2000). Pharmacology of ICF is complex and less well characterised than SICI and LICI. It is most likely a net facilitation arises from relatively stronger facilitation and weaker inhibition of intracortical circuits when excitatory post-synaptic potentials mediated by NMDA receptors (Schwenkreis et al. 1999; Ziemann et al. 1998) interact with the tail of $GABA_A$ receptor mediated inhibition (Hanajima et al. 1998).

Pharmacology studies demonstrate modulation of inhibitory $GABA_A$ receptor activity can affect the magnitude of ICF, as ICF was reduced following administration of the $GABA_A$ receptor agonist lorazepam (Ziemann et al. 1996a). The interaction between inhibition and facilitation was previously proposed as a mechanism underlying cortical reorganisation in lower-limb amputees (Chen et al. 1998a). This study also indicates these two mechanisms may be related as increased facilitation (ICF) and reduced inhibition mediated by $GABA_A$ receptors (SICI) were both observed in M1IPSI after amputation. Although mechanisms contributing to ICF are still uncertain, interactions between ICF and SICI in the amputee M1 are worthy of further investigation.

Neurophysiological measures were correlated with gait function in order to determine if patterns of cortical reorganisation were adaptive (good function) or maladaptive (poor function). For M1CON at both admission and walk, loss of inhibition (assessed by SICI) was associated with reduced step-width variability. Interestingly larger step-width variability is associated with amputees who experience falls (chapter five). Therefore, it is suggested loss of inhibition at admission and walk within M1CON may be adaptive and may help with gait function. For M1IPSI, loss of inhibition (assessed by SICI) at discharge was associated with greater step-length variability. It has previously been demonstrated that greater step-length variability is associated with amputees who experience falls (chapter five) and reduced community participation (chapter six). Therefore, loss of inhibition within M1IPSI at discharge is considered to be maladaptive. These findings suggest that ongoing reorganisation of M1IPSI after discharge may alter bilateral motor cortical control of the amputated limb. It is known that both M1CON and M1IPSI contribute to

motor control of the lower-limb in amputees (Cruz et al. 2003b; Simões et al. 2012). Contralateral predominance over ipsilateral corticomotor excitability is normal (see chapter seven of this thesis). Alteration to this balance of cortical control would likely affect function. It was previous identified in a study with chronic lower-limb amputees that upregulation of M1IPSI was associated with poor gait function (see chapter seven of this thesis). Although M1IPSI contribution to lower-limb motor control cannot be determined from this current study, previous work in upper-limb stroke indicates that ipsilateral reticulospinal pathways may upregulate following neurological injury (Ellis et al. 2007; Ellis et al. 2012; Schwerin et al. 2008). The reticulospinal pathway branches extensively as it terminate in the spinal gray matter (Matsuyama et al. 1999; Peterson & Abzug 1975), linking widely separated sections of the spinal cord (Lemon 2008). Increased activity in the reticulospinal tract would lead to non-specific activation of muscles producing motor conflict that may degrade prosthetic gait (Kagerer, Summers & Semjen 2003). If M1IPSI is upregulated after amputation similar to stroke, increased activity in putative reticulospinal projections for amputees may contribute to poor function.

There are limitations to this study which should be acknowledged. First, the sample size of the impending amputees is relatively small and limits interpretation of the findings. Recruitment of this population proved to be difficult within the limited time-frame. A post-hoc power calculation was performed for the impending amputees. As the hypothesis was corticomotor and intracortical excitability would change following amputation, MEP amplitude and SICI were used as outcomes before and after amputation. For M1CON, MEP amplitude had a power of 9% and SICI 20% indicating that the sample sizes used here were underpowered. For M1ipsi,

MEP amplitude had a power of 23% and SICI 98% indicating that the reported results for SICI were sufficiently powered. Second, this study was unable to access amputees immediately after amputation (mean, 10 days post amputation). This was due to the fact that patients were required to be medically stable before admission to the study. It is acknowledged that this may have confounded these results. However, before admission to the study, these amputees were not involved in rehabilitation which would contribute to a use dependent response of M1IPSI. Third, relatively low levels of SICI were observed in this study compared to other cortical representations. Differences observed between muscle representations are likely the result of functional specificity (Chen et al. 1998b). Additionally, the RF was pre-activated to a standardised and controlled level of activity. Muscle activation is associated with a reduction in inhibition (Ridding, Taylor & Rothwell 1995). Similar levels of intracortical inhibition have previously been reported in an active RF (Sidhu, Cresswell & Carroll 2013).

8.6 Conclusion

In conclusion, this study demonstrated bilateral reorganisation of M1 following lower-limb amputation. Inhibitory mechanisms in both M1CON and M1IPSI continue to be modulated through different phases of prosthetic rehabilitation. For M1CON, there was modulation of inhibitory GABAergic neurons assessed by SICI. For M1IPSI, there was modulation of inhibitory GABAergic neurons assessed by SICI and LICI. Disinhibition of M1CON at admission and walk appear to be an adaptive pattern of cortical reorganisation. However, disinhibition of M1IPSI at discharge appears to be maladaptive. Short-latency ICI appears to be an appropriate biomarker

of gait function in rehabilitating transtibial amputees. Future studies should investigate modulation of intracortical excitability during prosthetic rehabilitation to determine if gait function can be improved.

CHAPTER NINE: DISCUSSION AND FUTURE RESEARCH

About this chapter:

This chapter summarised key findings of the thesis which have addressed the four research questions identified in chapter two. Key findings are discussed in relation to the overall theme of the thesis which is *'novel assessments of gait and mobility function in transtibial amputees'*. Limitations of these studies are acknowledged, and future directions of research are outlined.

9.1 Discussion

Amputees represent an important group of patients in rehabilitation units, and successful restoration of gait and mobility function are key rehabilitation goals (Sansam et al. 2009). However, changing demographics and clinical characteristics observed in contemporary rehabilitation units may be affecting the ability to achieve these goals (Van Velzen et al. 2006). Therefore, detailed and new assessments of functional gait and mobility may provide useful information for both clinicians and patients to allow the development of new approaches to achieve optimal function. This thesis first sought to confirm how complex demographics and clinical characteristics of amputees affect rehabilitation outcomes by examining contemporary rehabilitation datasets. To further understanding, three novel assessments of gait and mobility function were then examined. These assessments sought to further characterise gait and mobility function. It was envisaged that these assessments would not only further understanding of amputee function, but may help to identify areas where new interventions could be developed and implemented to improve functional outcomes. There were several key findings from studies in this thesis which may contribute to characterising gait and mobility function in transtibial amputees. The first section of this thesis reviewed demographics, clinical characteristics and rehabilitation outcomes from contemporary amputee rehabilitation services, both nationally and at a single institute, to determine the extent and impact of challenges faced by rehabilitation units. The analyses found that age of amputees was decreasing, while number of comorbidities was increasing. These trends led to prolonged time to achieve key phases of rehabilitation such as prosthetic casting and independent walk. This finding supported the need for new

assessments of functional gait and mobility to further understand amputee rehabilitation. The second section explored three novel assessments of gait and mobility function. These were spatial-temporal gait variability, wearable technology and neurophysiological biomarkers of gait function. There were several important outcomes from these studies. First, greater variability of normalised spatial-temporal gait parameters was observed in amputees with falls history. Second, wearable technology was found to be a feasible method to assess activity and participation in the community. In addition, greater clinically assessed normalised gait variability was associated with reduced levels of community activity and participation. This further strengthened the value of adopting gait variability parameters as a functional measure of amputee gait. Finally, the potential contribution of altered motor control to gait function was investigated. Excitability of ipsilateral, relative to contralateral, descending projections were assessed as the measure ICE. Lower ICE values, indicative of stronger ipsilateral connectivity, were found to be associated with greater gait variability. Further, modulation of SICI in M1 at key phases of rehabilitation was found to be associated with gait function at discharge. Both ICE and SICI may be valuable neurophysiological biomarkers of gait function in transtibial amputees. The significance of these findings have been individually discussed within respective chapters of this thesis. This discussion will focus on addressing the specific research objectives outlined at the start of this thesis.

9.2 Challenges Facing Lower-Limb Amputee Rehabilitation Units in Australia

The first section of this thesis sought to establish a description of outcomes achieved by current Australian rehabilitation services at both a national level and a single hospital. Analysis of these datasets provided the clinical context and supported findings from the literature review demonstrating that amputee rehabilitation units in Australia are facing significant challenges to achieve optimal rehabilitation outcomes. The study in chapter three was the first to summarise a national dataset for amputee rehabilitation in Australia. Over the period of observation, there were year-to-year trends for increased LOS and a greater number of comorbidities for amputees entering rehabilitation. In chapter four the mobility marker, independent walk, was a key rehabilitation outcome for amputee rehabilitation which can be clinically monitored. Achieving independent walk is a significant rehabilitation milestone for gait and mobility function which is rarely reported in the literature. Characterising gait and mobility function is important in this population as the purpose of prosthetic rehabilitation is to optimise mobility to assist with community integration (Sansam et al. 2009). Achieving independent walk is perhaps the first step towards this and therefore should be considered an important milestone for gait function in amputee rehabilitation.

Time to achieve independent walk (and other rehabilitation milestones) was increasing over the period of observation, and is of concern for prosthetic rehabilitation units aiming to optimise gait and mobility function. The two studies in chapters three and four identified from year-to-year analysis that amputees were

becoming older, with the increased prevalence of comorbidities, in particular diabetes mellitus. While some interventions, such as the IPP and RRD, were able to reduce time to rehabilitation milestones, the overall trend was one of increased time to achieve independent walk. This is a concern for hospital efficiency, especially in an age where analysis of health systems and hospital efficiency are of importance (Hollingsworth 2008). The subsequent studies therefore sought to investigate assessments of amputee gait and mobility function. The purpose of these assessments was to further characterise amputee gait function in order to identify areas that could be targeted to improve prosthetic rehabilitation outcomes.

9.3 Speed Normalised Gait Variability is Associated with Falls History

Regaining prosthetic mobility is a challenging task for amputees. Previous studies demonstrate that a high proportion of both amputees undertaking rehabilitation (Pauley, Devlin & Heslin 2006), and community based amputees (Miller, Speechley & Deathe 2001) experience a fall. Findings from this thesis showed that from the cohort of community based transtibial amputees tested, 36% experienced a fall in the past 12 months. Falls are associated with negative consequences such as institutionalisation, hospitalisation, injury, and immobilisation (Stevens et al. 2006; Tinetti & Williams 1997). Therefore sensitive measures associated with falls are important for amputee rehabilitation clinicians. Spatial-temporal gait variability is one potential measure of gait function that may assist rehabilitation clinicians to identify falls risk. The significance of this measure was investigated in chapter five. There were two main findings. First, normalising spatial-temporal gait parameters for

walking speed is an important part of the process of characterising gait variability from spatial-temporal gait analysis in transtibial amputees. Second, the variability (coefficient of variation) of normalised spatial-temporal gait parameters of the amputated limb are associated with falls history in transtibial amputees. Therefore, walking speed normalised gait variability may be an important descriptor of deficiencies in gait control and should be considered for clinical use.

This study identified that normalised measures of step-time, step-length and step-width variability of the amputated limb were greater in fallers than non-fallers. Previous studies have identified step-time (Parker, Hanada & Adderson 2013) and swing-time (Vanicek et al. 2009) variability are greater in amputee fallers. However, the study in chapter five of this thesis is larger (n = 45) than those performed previously (n = 34, (Parker, Hanada & Adderson 2013); n = 11, (Vanicek et al. 2009)), and in addition, it was demonstrated that gait speed normalisation is an important technical aspect to consider when gait analysis is performed with repeated walk trials. It is important to consider normalising for walking speed as variation in speed has been shown to affect magnitude of spatial-temporal measures (Helbostad & Moe-Nilssen 2003). Common data collection protocols involve repeated walk trials to increase the step count that spatial-temporal parameters are calculated over, thereby improving reliability of mean measures (Lord et al. 2011b). However, in populations such as transtibial amputees, maintaining a constant speed for each trial is difficult. Variations in speed are therefore likely to affect accurate interpretation of spatial-temporal gait variability measures. The addition of speed normalisation in this study likely contributed to differences in findings between previous research and those presented here. Prior to normalisation, a number of additional measures,

including those previously reported, were found to be greater in transtibial amputee fallers. Following normalisation, only the three measures associated with the amputated side remained significantly greater in fallers. The results in chapter five support the suggestion that speed normalisation is an important technical consideration as a greater number of gait variability measures were different between fallers and non-fallers prior to normalisation.

It is difficult to conclude from this study why gait variability is associated with falls history in amputees. Gait variability quantifies fluctuations in the regularity of gait patterns which are relatively stable in healthy adults when walking over level ground (Gabell & Nayak 1984; Hausdorff et al. 1997). With a more variable gait pattern, the centre of pressure is likely to move over or beyond the base-of support in a relatively uncontrolled and unstable fashion which may predispose the person to experience a fall (Hausdorff 2005). Bipedal gait in humans is a sophisticated process involving coordination of multiple body systems (Winter 2009). Physiological factors that affect regulation of gait, and may subsequently increase gait variability include motor control (which was further investigated in chapters seven and eight) (Hausdorff et al. 1998; Herman et al. 2005), postural control (Parker et al. 2010), cardiovascular system (Hausdorff et al. 2003) and mental health (Hausdorff et al. 2001; Hausdorff et al. 2004; Herman et al. 2005). Many of these physiological systems may be altered following amputation. Furthermore, amputation of a limb affects normal gait. As a result of lower-limb amputation, proprioceptive feedback and propulsion are reduced (Bateni & Olney 2002). Amputee gait is characterised by a reduction in gait speed (Genin et al. 2008), increased metabolic cost of walking and decreased mobility endurance (Gailey et al. 1994; Genin et al. 2008; Sansam et al.

2009; Schmalz, Blumentritt & Jarasch 2002; Waters et al. 1976). These mobility difficulties are likely to contribute to increased gait speed variability in amputees, and also increased spatial-temporal variability.

The process of gait speed normalisation performed in this study is relevant for amputees and other populations where spatial-temporal gait analysis is performed. This study demonstrated normalised variability measures were significantly different to non-normalised measures. These findings indicate intra-subject gait speed variability should be accounted for to accurately interpret speed dependant parameters. Future studies investigating spatial-temporal gait analysis to assess gait function should therefore consider walking speed normalisation.

Clinical assessments of spatial-temporal gait variability can be performed using various instruments and procedures. These may include computerised walkways (Lord et al. 2011b), motion capture systems (Vanicek et al. 2009), and sensors worn on the body (e.g. gyroscopes (Najafi et al. 2009) and accelerometers (Hartmann et al. 2009b)). These instruments are currently unable to automate the process of walking speed normalisation when assessing gait variability which is a potential limitation to translating this technique to clinical practice. Future studies may investigate automated computer algorithms to reduce data processing time. However, results from this study indicate clinicians should consider gait analysis to identify amputees whose gait function may be more likely to contribute to a fall. In doing this, amputees likely to fall may be identified early, potentially preventing associated injury and hospitalisation (Stevens et al. 2006; Tinetti & Williams 1997).

Clinical analysis of gait function may have wider implications for rehabilitation clinicians seeking to restore functional levels of mobility and identify falls risk. It has previously been reported that higher levels of gait variability are associated with frailty (Montero-Odasso et al. 2011) and fear of falling (Rochat et al. 2010) in older adults. These factors may contribute to reduced community integration. This was further investigated in chapter six.

In summary, this study demonstrated normalised spatial-temporal gait variability is associated with falls history in transtibial amputees, and is therefore an important measure of gait function. In particular, normalised step-time, step-length and step-width variability of the amputated limb were demonstrated to be greater in amputee fallers compared to non-fallers. Characterising these measures during amputee rehabilitation may assist identification of amputees with poor gait function. In addition spatial-temporal gait variability analysis could be used clinically to determine effectiveness of interventions aimed at improving gait function.

9.4 Wearable Technology is Feasible to Assess Community Mobility Function

Techniques to accurately characterise community mobility function may be important to further understand amputee gait and mobility function, and assess effectiveness of prosthetic rehabilitation programs. Clinically assessed gait function may not only identify deficiencies in gait control, but may also be related to gait and mobility function in the community. Chapter six sought to investigate wearable technology to assess community mobility function and to further identify the

significance of clinical gait and falls assessments. Wearable technology was found to be a feasible method to assess community activity and participation in transtibial amputees. Clinical assessments of gait variability were related to levels of community activity and participation demonstrating importance for clinicians to assess amputee gait function. Unsurprisingly, community activity and participation was found to be lower in amputees with history of falls. These findings demonstrate an accurate method to assess community mobility function and further highlight significance of understanding clinical gait function and falls history in transtibial amputees.

Wearable technology devices are able to record data acquired during everyday tasks, and provide an accurate assessment of activity. The devices utilised in chapter six were a separate accelerometer based activity monitor (to assess step-counts) and GPS device (to assess location). Few previous studies have investigated use of wearable technology to assess mobility function in rehabilitation populations (Barzilay et al. 2011; Créange et al. 2007; Evans et al. 2012; Herrmann et al. 2011; Jayaraman et al. 2014; McCluskey et al. 2012; Storey et al. 2013). However given the recency of these publications, and continual technological improvements, it is likely that research into the application of wearable technology in rehabilitation will continue to expand, aiding translation to clinical practice. In addition, GPS devices are capable of providing additional data which may be important to assess gait and mobility function of various rehabilitation pathologies including transtibial amputees. Distance and speed can be obtained from commercially available GPS devices such as the one used in the current study. Distance is calculated between two individual latitude and longitude coordinates as a straight line. Although recordings are made

every five seconds for the device in the current study, it is possible that actual distance travelled between the two recordings may be greater if the participant did not travel in a straight line. Similarly speed is calculated as the distance travelled divided by the time between recordings (five seconds for the GPS device in this study). However, accurate assessment of speed may be influenced by inaccuracies of the distance measurement. Speed and distance would be important assessments of functional gait and mobility, and it likely more advanced technology will be able to record at higher frequencies, reducing discrepancies in distance and speed measures.

Gait variability was previously shown to be related to falls history (chapter five), but this current study identifies additional functional implications of higher levels of gait variability. Lower levels of community activity and participation were associated with greater normalised gait variability. Further, it was also identified that amputees with a history of falls were found to have reduced levels of community activity and participation. The exact nature of the contribution of falls history to reduced community activity and participation is unknown from this current study. However it is likely that amputees with a history of falls may experience greater fear of falls (Tinetti et al. 1994b), potentially reducing confidence to participate in the community. It is difficult to determine if wearable technology could be used as a tool to predict falls risk in amputees. Previous studies have identified that fear of falls restricts mobility and social integration (Howland et al. 1998; Tinetti et al. 1994b; Vellas et al. 1997). Therefore, it is most likely that fear of falls restricts community activity and participation, and not activity and participation leading to increased risk of falls. However, further investigation would be required to confirm this.

Optimising attainment of community activity and participation should be a primary rehabilitation goal for clinicians. Regularly monitoring clinical gait function and assessing falls history may not only assist identification of falls risk and prevent negative consequences of falls, but may lead to improved mobility related quality of life. Interventions to reduce gait variability or falls risk such as moderate exercise (Krebs, Jette & Assmann 1998; Province et al. 1995), vibrotactile stimulation (Galica et al. 2009) or multifactorial interventions (adjust medications, exercise and behavioural instructions) (Tinetti et al. 1994a) may not only have implications for falls, but result in greater community integration.

In conclusion, wearable technology has future potential as a tool for field assessment of mobility function in transtibial amputees. The study in chapter six of this thesis demonstrated wearable technology was able to accurately assess community activity and participation over a seven day period. Clinical measures of gait variability were negatively associated with community activity and participation, suggesting assessment of gait function is important. Similarly, falls history was associated with reduced community activity and participation. Monitoring falls and reducing falls risk may have important implications for mobility related quality of life. Future clinical practice should consider implementation of wearable technology as a novel assessment tool of mobility function in the community.

9.5 TMS Measures as Neurophysiological Biomarkers of Gait Function

The studies in chapters seven and eight sought to identify neurophysiological biomarkers of gait function. Key findings from these studies were that the measure ICE, a ratio of corticomotor excitability of contralateral and ipsilateral descending projections to the amputated limb, was lower in amputees than in control subjects. The measure ICE was associated with gait function, and therefore is likely to have good potential as a biomarker of gait function in this population. For amputees, lower ICE values (greater contribution of ipsilateral, relative to contralateral, projections to the amputated limb) were associated with increased normalised gait variability. This pattern of cortical reorganisation was associated with poor gait function as normalised gait variability was greater in amputee fallers (chapter five), and associated with reduced levels of community participation (chapter six). In chapter eight, intracortical excitability of M1 was investigated in both cortical hemispheres. There were several novel findings that were important to the understanding of TMS biomarkers of gait function in this population. Following unilateral transtibial amputation there was bilateral M1 reorganisation which continued throughout prosthetic rehabilitation. A reduction in GABAergic inhibition was an identified mechanism mediating bilateral M1 reorganisation. GABAergic inhibition at key rehabilitation phases was related to gait function at discharge, and may be an appropriate biomarker of function, however further studies are required to confirm this. These findings provide important novel contributions to understanding cortical reorganisation and motor control associated with gait function in transtibial amputees.

9.5.1 ICE as a neurophysiological biomarker of gait function

Human motor control of locomotion differs from animal models as there is a greater cortical contribution to controlling motion of the lower-limbs. There are several lines of evidence which support this. First, M1 lesions have greater detrimental effects on gait function in humans compared to animals (Porter & Lemon 1993). Second, human functional MRI studies demonstrate increased M1 activation during locomotion (Fukuyama et al. 1997). A cortical contribution to human locomotion is necessary due to more complex bipedal gait patterns, and greater requirement of variability and adaption of gait than in animals (Capaday et al. 1999; Duysens & Van de Crommert 1998; Jahn et al. 2008; Jordan 1998; Nielsen 2003). Identifying neurophysiological biomarkers of gait function from M1 corticomotor excitability using TMS is therefore justified based on these findings that M1 is integral for gait control.

The study in chapter seven identified that for both healthy adults and transtibial amputees there is an important bilateral cortical contribution to lower-limb function. This new finding confirms previous functional MRI studies which demonstrated there is bilateral activation of M1 during lower-limb motor control (Luft et al. 2002; Sahyoun et al. 2004). Findings from chapter seven of this thesis progress understanding of human motor control as it was found that the relative balance of excitability between $M1_{CON}$ and $M1_{IPSI}$ is important for normal gait function. Negative ICE, which indicates relatively greater excitability of ipsilateral projection from $M1_{IPSI}$, was related to poor function (greater step-time variability). It is acknowledged that regression models used to demonstrate this relationship only

reveal associations between neurophysiological measures and gait function and a causal relationship cannot be assumed. It is impossible to decipher from the current study if cortical reorganisation is responsible for poor function, or whether poorly re-trained gait patterns after amputation drive plasticity in M1. Regardless, lower ICE values indicate a pattern of cortical reorganisation which is associated with poor gait function, as increased step-time variability is associated with falls history and reduced community participation. Therefore, ICE is likely to be a suitable neurophysiological biomarker of gait function which could be used clinically to identify amputees with likely poor recovery of gait function at discharge from rehabilitation.

Currently, ICE as a cortical biomarker of gait function in community dwelling transtibial amputees may have limited clinical practicality. In this study ICE was assessed on community dwelling amputees who were already provided with a prosthesis and were capable of completing functional gait analysis. In this instance it would be easier to simply complete spatial-temporal gait analysis if the required equipment were available (i.e. a computerised walkway system). However, ICE may have greater clinical value as a biomarker of gait function for amputees in the rehabilitation phase, prior to prosthetic provision. Further studies would be required to confirm the value of ICE for this purpose. Alternatively, future studies seeking to improve gait function by modulating M1 excitability may use ICE as a functional neurophysiological measure to identify amputees requiring intervention and determine the effectiveness of treatment interventions. The potential of ICE to assist clinical practice should be further investigated.

It is most likely that the pathway involved in upregulation of ipsilateral projections is the ipsilateral cortico-reticulospinal tract. Previous studies in stroke suggest this could be the descending pathway activated when ipsilateral responses to TMS are observed from the contralesional M1 (Ellis et al. 2007; Ellis et al. 2012; Schwerin et al. 2008). Reticulospinal projections descend to the spinal cord, innervating axial and proximal spinal motoneurons important for the control of muscles subserving locomotion (Drew, Prentice & Schepens 2004). In contrast to the precise innervation of motoneurons by corticospinal projections, reticulospinal axons branch extensively as they terminate in the spinal cord (Matsuyama et al. 1999; Peterson & Abzug 1975). These widespread terminations would activate many motoneuron pools leading to non-specific activation of muscles that may degrade prosthetic gait. In this manner, upregulated ipsilateral corticomotor projections could produce motor conflict in the spinal cord (Kagerer, Summers & Semjen 2003). Motor conflict would arise as normal gait patterns require asymmetrical movement of the lower-limbs. In lower-limb amputees with negative ICE values, ipsilateral projections would likely interfere with contralateral projections driving motoneurons innervating residual muscles of the amputated limb. These interfering signals may disturb the normal rhythmic sequencing and timing of gait leading to increased variability of the stepping pattern and compromising function. It is possible the cortico-reticulospinal tract is implicated in upregulated ipsilateral corticomotor projections observed in these amputees.

9.5.2 SICI as a neurophysiological biomarker of gait function

Similar to ICE, SICI is a neurophysiological measure which was shown to be related to gait function, and may be a suitable biomarker of function. Short ICI is thought to

be a measure of $GABA_A$ergic inhibition (Di Lazzaro et al. 2000; Di Lazzaro et al. 2005a; Di Lazzaro et al. 2005b; Ziemann et al. 1996a). Reduced excitability of inhibitory $GABA_A$ergic interneurons was observed at different phases of amputee rehabilitation for M1 bilaterally. Importantly, the neurophysiological measure SICI was related to gait function at discharge. Reduced SICI in M1CON at the time of admission and walk indicated adaptive neuroplasticity, as reduced SICI at these phases was associated with reduced gait variability at discharge indicating better function. Conversely, reduced SICI in M1IPSI at discharge indicated maladaptive neuroplasticity, as reduced SICI was associated with increased gait variability at discharge. For M1CON, the use of SICI as a cortical biomarker of gait function has important clinical implications, as the functional assessment was performed at a later time than the neurophysiological assessment. Therefore, if SICI was to be assessed prior to provision of a prosthesis and reduced SICI was not observed in this hemisphere, then rehabilitation programs may be modified or interventions could be targeted to ensure optimal gait function is achieved at discharge.

For M1CON, the adaptive pattern of reduced SICI at time of admission to rehabilitation appears to be a cortical response to the amputation itself, and may be associated with expansion of neighbouring representations within M1 (Cruz et al. 2003b; Lotze et al. 2001; Simões et al. 2012). This study demonstrated that SICI was reduced following amputation. Prior to amputation there were no significant differences in corticomotor and intracortical excitability between impending amputees and controls. Therefore, the reduced SICI observed in this study is most likely related to the amputation. However, the adaptive pattern of reduced SICI at time of walk may be a use-dependent response, as this is the first time amputees

begin walking with a prosthesis. Reduction of excitability of GABAergic inhibitory interneurons has previously been associated with motor learning (Perez et al. 2004; Stagg, Bachtiar & Johansen-Berg 2011). The complexities of prosthetic gait are therefore likely to induce a cortical motor learning response. It is difficult to determine why a reduction in SICI in M1CON would not be observed at admission or walk in some amputees in this study (i.e. a maladaptive pattern of reorganisation). Potential explanations may be related to severity and duration of the vascular disease or lack of adequate prosthetic mobility training. Alternatively, some amputees may have reduced capacity for plasticity relating to a number of characteristics such as age, gender, and genetics (Ridding & Ziemann 2010). Further studies would be required to investigate these factors.

For M1IPSI, the maladaptive pattern of reduced SICI may indicate that ongoing reorganisation within that hemisphere is detrimental to function. Similar observations were made in chapter seven where relatively greater corticomotor excitability of descending ipsilateral projections evoked from M1IPSI were associated with poor gait function. The likely contribution of the ipsilateral cortico-reticulospinal tract to poor function has been discussed previously.

9.5.3 Neurophysiological biomarker summary

In summary, the neurophysiological measures ICE and SICI appear to have potential as cortical biomarkers of gait function in transtibial amputees. The bilateral nature of reorganisation following lower-limb amputation implies corticomotor and intracortical excitability of either or both M1s may be used as a biomarker of gait function. These studies demonstrated that reduced SICI in M1CON at admission to

rehabilitation and walk are adaptive patterns of cortical reorganisation as they were associated with better gait function as characterised by gait variability. However, reduced SICI in $M1_{IPSI}$ at discharge was indicative of poor gait function. Reduced SICI in $M1_{IPSI}$ may lead to ongoing cortical reorganisation and would likely increase corticomotor excitability. In theory this could lead to reduced ICE values as observed in community amputees which were also indicative of poor gait function. These findings have implications for clinical practice as these potential biomarkers may assist identification of amputees requiring assistance to optimise gait function. Future studies may also investigate neurophysiological interventions aiming to drive cortical plasticity towards adaptive patterns and improve gait function. This possibility is discussed as a future research direction (section 9.7).

9.6 Limitations

This thesis comprises a number of studies which have investigated characteristics of gait and mobility function in transtibial amputees. Limitations specific to each study have been discussed in the relevant chapters. However there are some limitations pertaining to the overarching theme of this thesis which should also be considered when interpreting these findings.

Firstly, participants of the studies in chapters four to eight were primarily recruited from one hospital setting. In addition, unilateral transtibial amputees were specifically selected to eliminate the influence that level of amputation may have on gait and mobility function. Results may therefore not be generalisable to other hospital settings, prosthetic services or levels of amputation. However, demographics

and clinical characteristics of the single hospital setting where participants were recruited from were similar to that observed at a national level (see chapter three), thereby providing some confidence that findings of this thesis are representative of the larger population of transtibial amputees. Second, limited data of prosthetic componentry was obtained. However, for the studies in chapters four and eight, amputees were undertaking prosthetic rehabilitation and their prosthetic componentry was standardised as all amputees received an interim prosthesis (described in chapter four). For studies in chapters five, six and seven, fit and comfort of the prosthesis were confirmed with participants and their prosthetists prior to inclusion. It is possible that prosthetic foot componentry and suspension systems may have varied between participants in these studies, and therefore may have influenced gait and mobility function to some degree. However, prosthetic foot componentry and suspension systems were individually prescribed by the prosthetics department and were specified to the participant's functional capabilities and requirements. In addition, the prosthetic componentry for each participant was not altered during the duration of the studies in this thesis.

For analysis of gait variability (chapter five), it has previously been suggested that hundreds of steps are required for accurate analysis (Hollman et al. 2010). In this study ten walking trials were performed which captured a range of step counts depending on participant step lengths (range 34-110 steps). Although a limitation of this study is that the recommended step counts to assess gait variability were not achieved, attempting to do so with amputees would likely have resulted in fatigue for many participants, potentially confounding analysis of spatial-temporal parameters (Helbostad et al. 2007). Future studies which attempt to implement gait variability as

an assessment of gait function in transtibial amputees should consider fatigue effects of performing high numbers of walk trials.

This thesis obtained a retrospective falls history for the studies in chapters five and six. This method of obtaining falls data relies on participant recall and memory, which may have biased results. These studies would have benefited from a prospective design to obtain falls data. A prospective study would be less affected by participant recall and would enable the assessment of the predictive ability of normalised gait variability. This would be of greater value to amputee rehabilitation as gait variability would identify amputees with increased falls risk, rather than history of falls. However, due to time constraints of completing this thesis, a retrospective study was performed.

In relation to the study in chapter six, the limitations of GPS devices, which include loss of satellite signal and requirement for frequent battery charging, have previously been identified. However, these are important limitations that impact on the implementation of GPS devices to assess mobility function in transtibial amputees. With future advancements in technology it is likely the significance of these limitations will reduce, but will still need to be considered when using these devices clinically. Furthermore, this study assessed community activity (community step counts) and participation (community visits). Activity and participation are broad categories. Measures of step counts and community visits were used as proxy measures of activity and participation respectively. It should be acknowledged these proxy measures may not encompass all aspects of activity and participation. Despite

this, assessment of community based step counts as a proxy for activity is an appropriate choice for this thesis given the theme of mobility and gait function.

For the TMS studies in chapters seven and eight, it should be acknowledged that corticomotor and intracortical excitability were only assessed for the RF muscle representation. Although RF plays an important role in lower-limb motor control related to gait function, there are many other muscles which contribute to locomotion (Kwon et al. 2003). However, due to the level of amputation, this study was limited to muscles proximal to the knee. The two main muscle groups proximal to level of amputation were the quadriceps and hamstring muscles. Positioning surface EMG electrodes over the hamstring muscle may have resulted in signal interference with participants in a seated position. Furthermore, pre-activating the hamstring muscle would have required movement, possibly inducing surface EMG signal interference. In addition, collecting data from both the hamstring and quadriceps muscles would have substantially increased data collection time as it is difficult to co-contract both muscle groups (as TMS measures were assessed during an active muscle contraction). Therefore a separate series of experiments to collect hamstring data would have been required. Given the current duration of data collection for one muscle only (90 – 120 minutes), muscle selection was limited to the quadriceps, from which the most superficial muscle (rectus femoris) was selected.

As stated for the TMS studies, MEPs in the lower-limb were difficult to elicit and required pre-activation to evoke a MEP of acceptable amplitude. Assessing corticomotor and intracortical excitability in pre-activated muscles introduces a number of factors to consider to ensure reliable data interpretation. One of the most

significant concerns is that background (pre-stimulus) rmsEMG may not be consistent between compared measures. Muscle activity required for knee extension on the amputated limb was less without the weight of the limb; therefore differences would exist in rmsEMG between the two limbs. Although differences in rmsEMG did not reach statistical significance, the differences may have affected corticomotor and intracortical excitability measures. Future studies wishing to further investigate neurophysiological measures with lower-limb amputees should bear this limitation in mind. This is of particular importance for studies investigating pre to post measures of the amputated limb, or when comparing MEPs between the amputated and non-amputated limb. Muscle activity during the knee extension task is likely to be less compared to pre amputation or to the non-amputated limb due to a shortening of the lever arm and reduce weight of the limb. In addition, inactivity of the amputated limb may diminish muscle strength, further reducing muscle activity of that limb.

Finally, in the literature review it was identified that the cortex, brainstem and cerebellum contribute to motor control of gait patterns in humans (Duysens & Van de Crommert 1998). However, studies in this thesis only investigated M1 corticomotor and intracortical excitability as biomarkers of function. Contribution of the brainstem and cerebellum were not investigated despite their involvement in human locomotion. This is a limitation of TMS, and other neurophysiological techniques such as functional MRI would be required to investigate the influence of these motor regions.

9.7 Future Research Directions

Studies within this thesis have identified new characteristics of gait and mobility function using three novel assessments in transtibial amputees. There are several studies which may be conducted to follow on from these findings, potentially confirming clinical relevance and application of these functional assessments. The future research directions will be discussed for each of the three functional assessments.

In chapter five of this thesis it was identified that normalised gait variability parameters were associated with falls history. A future study should investigate normalised gait variability as a predictor of falls. This would require normalised gait variability to be assessed, followed by provision of a falls diary to record any subsequent falls over the period of interest. Similar studies with falls diaries have been performed previously (Paterson, Hill & Lythgo 2011). A prospective study would demonstrate predictive ability of normalised gait variability and may provide greater clinical relevance for assessment of gait variability. Further studies could determine why normalised gait variability is increased in transtibial amputees with history of falls. This thesis investigated aspects of motor control, however other potential contributions exist. Further investigation of these contributions may guide interventions to improve amputee gait function and risk of falls.

Future studies may seek to determine if wearable technology is appropriate for guiding prosthetic componentry prescription. In the current study in chapter six it was demonstrate that commonly used assessments to guide prosthetic prescription,

the K level classification (Health Care Financing Administration 2001) and AMP-PRO tool (Gailey et al. 2002) were unable to correctly differentiate higher functioning amputees for activity and participation in the community. Although there is some ambiguity, it is generally considered that prescription of prosthetic componentry should be determined by activity requirements and abilities of the amputee (Van Der Linde et al. 2004a). Using accurate objective measures of community based activity and participation are likely to be more reliable for assessing mobility function in amputees than current methods. Therefore wearable technology has potential as an assessment to assist and guide prosthetic prescription, and should therefore be investigated.

While wearable technology was able to identify that K levels may not accurately differentiate functional abilities of higher functioning amputees, there is potential to perform similar studies with different clinical assessments. Further studies may choose to utilise wearable technology as a 'gold standard' to validate other clinical assessments of gait and mobility function. These assessments may be either currently used measures, such as the special interest group in amputee medicine mobility grades (Ryall et al. 2003), or may be developed in the future to assess amputee activity and participation. As signals from wearable technology are recorded continuously it is likely they will contain valuable information about the activities and movements performed which could be compared to clinical measures and scales.

Finally, there are a number of future studies which should be conducted in relation to the findings from chapters seven and eight. In chapter seven it was identified that the neurophysiological measure ICE may be a biomarker of gait function in transtibial

amputees. However, results from this study were unable to determine whether corticomotor excitability patterns were responsible for gait function, or whether gait patterns drive cortical plasticity. Future studies should seek to examine this mechanism. This may be achieved by reducing cortical excitability of M1IPSI and determining the effect on gait function, perhaps using non-invasive brain stimulation techniques. By reducing excitability of M1IPSI, corticomotor excitability of descending projections evoked from M1IPSI would also reduce, thereby increasing ICE. If increased ICE improved gait function (reduced gait variability), then this would provide new evidence to suggest that corticomotor excitability affects gait function.

There are a number of neuromodulatory techniques which may reduce excitability of M1IPSI. Perhaps the most common are transcranial direct current stimulation, repetitive TMS, and paired associative stimulation which are all capable of bi-directionally modulating M1 excitability (Ziemann et al. 2008). Transcranial direct current stimulation involves a weak polarising current which is applied to alter neuronal membrane potential, with after effects that may last several minutes (Nitsche et al. 2003; Nitsche & Paulus 2000; Nitsche & Paulus 2001). Repetitive TMS protocols involve a train of pulses spaced by identical inter-stimulus intervals (simple repetitive TMS), or differing inter-stimulus intervals (pattered repetitive TMS). Depending on pulse configurations, frequencies, stimulus intensity, number of pulses and duration, the effect may be increased or decreased cortical excitability (Ziemann et al. 2008). Paired associated stimulation is a paradigm involving low-frequency, repetitive nerve stimulation combined with TMS over the contralateral M1. If a weak synaptic input repeatedly arrives at a neuron shortly before the neuron

fires an action potential, strength of the synapse increases. Where the weak synaptic input arrives shortly after the neuron fires, then strength of the synapse decreases (Stefan et al. 2000; Ziemann et al. 2008). These techniques may be applied to modulate cortical excitability to potentially improve gait function and may elucidate some of the cause and effect relationships identified in this thesis.

Future studies seeking to modulate corticomotor excitability of M1 lower-limb representations to increase ICE, and improve gait function, may face similar challenges to those in the current study of preferentially stimulating one hemisphere. Lower-limb cortical representations are located close to the interhemispheric fissure, and the ipsilateral and contralateral M1 representations are therefore in close proximity to each other. As ICE is a ratio between excitability of both hemispheres, it would be preferential to independently modulate cortical excitability of one hemisphere. An alternative possibility to modulate M1 excitability may be cerebellar stimulation. Stimulation over the cerebellum is capable of modulating M1 excitability through the cerebello-thalamo-cortical pathway, which inhibits a tonic facilitation on M1 (Di Lazzaro et al. 1994; Ugawa, Hanajima & Kanazawa 1994; Ugawa et al. 1997). Previous studies have identified that transcranial direct current stimulation over the cerebellum is capable of modulating M1 excitability, and improving motor function of the lower-limb (Shah, Nguyen & Madhavan 2013).

The study in chapter eight identified that SICI may be a potential biomarker of gait function in transtibial amputees undertaking prosthetic rehabilitation. Future studies should utilise SICI as a biomarker of function and identify amputees who may benefit from neuromodulation to promote adaptive patterns of plasticity. At

completion of rehabilitation, gait function should be assessed to determine how effective neuromodulation is at improving gait function. Similar techniques may be used to modulate SICI in M1. It has previously been demonstrated that cathodal transcranial direct current stimulation can increase intracortical inhibition (Batsikadze et al. 2013; Kidgell et al. 2013), while anodal transcranial direct current stimulation can reduce intracortical inhibition (Cengiz, Murase & Rothwell 2013; Kidgell et al. 2013) in the healthy human brain. Repetitive TMS protocols also modulate intracortical inhibition. A specific repetitive TMS paradigm known as theta burst stimulation was found to bi-directionally modulate intracortical inhibition (Huang et al. 2005). Intracortical inhibition increases following intermittent theta burst stimulation, and decreases following continuous theta burst stimulation (Huang et al. 2005). Both transcranial direct current stimulation and theta burst stimulation studies to modify cortical excitability should be investigated to test the use of SICI as a biomarker of gait function.

9.8 Conclusion

Contemporary amputee rehabilitation units are facing unique challenges with younger, more comorbid amputees entering rehabilitation and requiring greater LOS to achieve optimal levels of gait and mobility function. With increasing incidence of diabetes mellitus, lower-limb amputees are likely to remain a small, but significant patient group in rehabilitation units. Restoration of gait and mobility function are key rehabilitation goals (Sansam et al. 2009), and greater understanding of gait and mobility will likely increase understanding of amputee function and may lead to novel interventions to improve function. New and accurate methods to assess gait

and mobility function are critical to the field of amputee rehabilitation, and this thesis has examined several novel assessments. First, the variability of spatial-temporal gait parameters of the amputated leg which were normalised to walking speed were associated with falls history. These gait variability parameters were used as a marker of gait function. Given the substantial proportion of amputees who experience a fall, measures associated with falls are important. Second, wearable technology was capable of assessing community mobility function over an extended period. Objective data obtained from the devices is likely to assist clinical decisions and enhance understanding of amputee mobility function. In this thesis it was identified that increased levels of gait variability and falls history were related to reduced community activity and participation. These findings highlight the importance of clinical gait and falls assessments. Finally, two neurophysiological biomarkers of gait function for amputees were identified. Both ICE and SICI may assist clinicians by identifying amputees with poor gait function who require additional gait therapy, or alternatively, neuromodulatory interventions to promote adaptive patterns of neuroplasticity. Future studies should continue to investigate the clinical significance of the assessments of gait and mobility function presented herein to aid their translation to clinical practice and assist with identifying potential interventions to improve function in transtibial amputees.

APPENDICES

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Appendix 1

HEALTH SERVICES RESEARCH

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Feature

Lower-limb amputee rehabilitation in Australia: analysis of a national data set 2004-10

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Abstract

Objective. Examine demographics, clinical characteristics and rehabilitation outcomes of lower-limb amputees, using the Australasian Rehabilitation Outcomes Centre (AROC) database.

Methods. Lower-limb amputee rehabilitation separations between 2004 and 2010 were identified using AROC impairment codes 5.3–5.7.[1] Analysis was conducted by year, impairment code, Australian National Sub-acute and Non-Acute Patient (AN-SNAP) classification (S2–224, Functional Independence Measure (FIM) motor(Mot) score 72–91; S2–225, FIM (Mot) score 14–71) and states of Australia.

Results. Mean length of stay (LOS) for all lower-limb amputee episodes was 36.1 days (95% confidence interval (CI): 35.4–36.9). Majority of episodes were unilateral below knee (63.6%), males (71.8%) with a mean age of 67.9 years (95% CI: 67.6–68.3). Year-on-year analysis revealed a trend for increasing LOS and decreasing age. Analysis by impairment code demonstrated no significant difference in rehabilitation outcomes. Analysis by AN-SNAP found that LOS was 16.2 days longer for S2–225 than for S2–224 (95% CI: 14.7–17.8, $P < 0.001$), and FIM (Mot) change was 12.0 points higher for S2–225 than for S2–224 (95% CI: 11.5–12.6, $P < 0.001$). Analysis by states revealed significant variation in LOS, FIM (Mot) change and FIM (Mot) efficiency which may be associated with variations in organisation of rehabilitation services across states.

Conclusion. Although amputees represented a comparatively small proportion of all rehabilitation episodes in Australia, their LOS was significant. Unlike many other rehabilitation conditions, there was no evidence of decreasing LOS over time. AN-SNAP classes were effective in distinguishing rehabilitation outcomes, and could potentially be used more effectively in planning rehabilitation programs.

What is known about the topic? Literature reporting on the rehabilitation outcomes of cohorts of lower-limb amputees in Australia is limited to individual sites. No previous literature was identified that reported national data.

What does this paper add? This study investigates amputee rehabilitation at a national level over a 7-year observation period (2004–10) and comprises 6588 episodes. It reports the national demographics, clinical characteristics and rehabilitation outcomes, with the aim of identifying findings that have implications for practitioners.

What are the implications for practitioners? Although only a small proportion of all episodes in the AROC database, this subset of lower-limb amputee episodes has provided a useful snapshot of the current state of amputee rehabilitation in Australia. We believe these findings have significant implications for practitioners in delivery of amputee rehabilitation services across Australia. Practitioners may benefit from adjusting service delivery based upon the decreasing age of lower limb amputees. Findings from this study also indicate that AN-SNAP classifications are effective in discriminating amputee rehabilitation outcomes and may be used to streamline rehabilitation services and provide a more efficient and effective rehabilitation service to prevent further increases in LOS.

Additional keywords: AN-SNAP classification, Functional Independence Measure, FIM Motor, rehabilitation centres, rehabilitation outcome.

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Introduction

Worldwide incidence of lower-limb amputation is highly variable with incidence rates ranging from 5.8 to 31 per 100 000.[2] Most lower-limb amputees in the developed world are elderly dysvascular patients often presenting with diabetes mellitus.[3–5] It is estimated that 700 000 Australians (3.6% population) were diagnosed with diabetes mellitus, and 3394 diabetic related lower-limb amputations were performed in Australia in 2004–05.[6]

Amputees are a core group in Australian rehabilitation units who have a long index length of stay (LOS). The long LOS associated with the index admission is justified by clinicians as important because restoring independent mobility and community integration reduces the larger social and health service costs associated with disability.[7] It is widely believed that growth of interventional vascular surgery has helped reduce or postpone lower-limb amputation numbers in dysvascular patients.[8,9] However, it isunknown whether amputees entering rehabilitation units now present with different demographics than previously. This may result in a change in the outcomes achieved, time taken to achieve these outcomes or in the nature of the clinical programs provided. National outcome data collected by the Australasian Rehabilitation Outcomes Centre (AROC) will allow further investigation into the demographics, clinical characteristics and rehabilitation outcomes across Australia.

AROC collects standardised data for each and every episode of inpatient rehabilitation care from rehabilitation services in Australia (private and public). It provides a national benchmarking service, as well as information to improve understanding of factors that influence rehabilitation outcomes and costs. The objective of this study was to examine the AROC database for inpatient lower-limb amputee rehabilitation episodes to understand the demographics, clinical characteristics and rehabilitation outcomes. Service implications for lower-limb amputees in Australia will be drawn from these findings. The primary outcomes of interest will include improvement in patient functional status, hospital LOS, clinical characteristics and discharge destination. In addition, the yearly trends in episode outcomes and service efficiency will be examined, as well as comparison of outcomes for service provision between impairment codes, Aus-tralian National Sub-Acute and Non-Acute Patient (AN-SNAP) classifications, and States of Australia.

Methods

Design

This study was a retrospective analysis of lower-limb amputee rehabilitation outcomes for separation episodes between 2004 and 2010 using the AROC database. Lower-limb amputee data were identified using AROC impairment codes 5.3 to 5.7[1] (Table 1). All data were de-identified before data extraction and analysis. Ethical approval for this study was provided by the Southern Adelaide Clinical Human Research Ethics Committee.

AROC dataset

AROC was established in July 2002 as a joint initiative of the Australasian Rehabilitation sector and is funded by contributions from all stakeholders, including facilities, health funds, Department of Veterans' Affairs, health departments (state and commonwealth), some general insurers and the Australasian Faculty of Rehabilitation Medicine (AFRM). AROC receives quarterly episodic data from private and public rehabilitation facilities across Australia. Thirty facilities were submitting data to AROC in 2002. However AROC coverage grew steadily with 109 facilities submitting by 2004, and 180 by 2011, representing more than 95% of Australian rehabilitation facilities and inpatient episodes. Of the rehabilitation facilities submitting data toAROC, 21 units specialise in lower-limb amputee rehabilitation and contributed the majority of amputee episode data (59.3%). The AROC dataset includes 42 items: sociodemographic, funding and employment details, episode items (admission and dis-charge), medical (impairment codes, comorbidities, complica-tions), and outcome data (patient level of function at admission and discharge).[10,11]

Data within the AROC database are classified under the AN-SNAP casemix classification system, which was developed at the

Table 1. Definition of AN-SNAP and impairment codes used for lower-limb amputees

Term	Definition
AN-SNAP code:	
S2–224	Functional Independance Measure motor score 72–91
S2–225	Functional Independance Measure motor score 14–71
Impairment code:	
5.3	Unilateral amputation above knee or through the knee
5.4	Unilateral amputation below the knee
5.5	Bilateral amputation, both above knee or through knee
5.6	Bilateral amputation, one above or through the knee, one below the knee
5.7	Bilateral amputation, both below the knee

University of Wollongong in 1997.[10] The purpose of AN-SNAP was to provide a casemix classification system for sub and non-acute care provided in several treatment settings. It was borne out of a growing recognition that patients should be classified by functional ability, rather than by diagnosis and procedure codes as in the acute sector.[11] AN-SNAP subdivides case episodes accord-ing to both diagnosis and functional level, using the Functional Independence Measure (FIM). Version 2 AN-SNAP classifica-tion became operational in 2007[11] and includes 45 inpatient rehabilitation classes. For amputees, AN-SNAP version 2 con-tains two functional levels based on the FIM motor (FIM (Mot)) score. The two functional classes are S2–224 (FIM (Mot) 72–91) and S2–225 (FIM (Mot) 14–71). FIM is an internationally recognised and reliable functional-status instrument that is widely used with rehabilitation inpatients.[12–15] It contains 18 items, 13 of which relate to motor function, and five to cognition. Total FIM scores including both motor and cognitive aspects range from 18 to 126, with higher scores representing greater functionality. FIM scores relating to motor assessments range from 13 to 91. AROC holds a territory licence for use of the FIM in Australia and New Zealand, and is responsible for the national certification and training for all accredited rehabilitation clinicians. Clinical staff are required to be recredentialed in the FIM every 2 years to maximise the quality of data. All data received by AROC are screened for errors and missing data before adding the episodes to the database. If necessary, AROC will request that the submitting facility review and correct any inconsistencies.

Analysis

De-identified lower-limb amputee rehabilitation episodes be-tween 2004 and 2010 were extracted from the main AROC database using AROC impairment codes 5.3–5.7.[1] Data were then transferred to SPSS version 19.0 for analysis. Descriptive analysis was conducted on demographics, FIM (Mot) (admission score, discharge score, change and efficiency), LOS, clinical characteristics and discharge destination collated by year, AN-SNAP classification, impairment code and States of Australia. FIM (Mot) change is the difference between admission and discharge FIM (Mot) scores, and is an indicator of change in functional status during rehabilitation stay. FIM (Mot) efficiency is the FIM (Mot) change achieved per day of LOS. Significant differences were analysed by independent sample *t*-tests and between-subjects analysis of variance (ANOVA) with *post-hoc* pairwise comparisons using Tukey adjustments for significant results. Results of descriptive analysis are presented as a mean and 95% confidence interval (95% CI). Results of independent sam-ple *t*-test and ANOVA are presented as mean difference and 95% CI.

Results

Episodes

A total of 6588 lower-limb amputee episodes were submitted to the AROC database between 2004 and 2010. However only 4864 (73.8%) of episodes could be analysed for rehabilitation out-comes, which requires valid LOS and valid FIM scores. Of all rehabilitation episodes submitted to the AROC database between 2004 and 2010, lower-limb amputees contributed only 1.7% of episodes (see Table 2). Of all submitted amputee episode data, New South Wales (NSW) was the largest contributing state (48.5%), whilst the majority of episodes were submitted from public facilities (83.4%). The number of lower-limb amputee episodes submitted to the AROC database grew steadily each year as did the number of facilities submitting lower-limb amputee episodes data, reaching 99 by 2010.

Demographics

The majority of lower-limb amputee episodes were male (71.8%), with mean age of all episodes being 67.9 years (95% CI: 67.6–68.3). Episodes in the private sector had a mean age 6.1 years lower than those in the public sector (95% CI: 5.1–7.0, $P < 0.01$). Episodes categorised to the higher functioning AN-SNAP class (S2–224) had a lower mean age by 10.0 years than did those in S2–225 (95% CI: 9.2–10.8, $P < 0.001$). Year-on-year analysis revealed a trend for decreasing age, with the mean age in 2004 being 70.2 years (95% CI: 69.1–71.3), dropping in 2010 to 67.1 years (95% CI: 66.2–68.0).

Clinical characteristics

The majority (63.6%) of episodes within the AROC database were unilateral below-knee amputees, with most episodes being the lower functioning AN-SNAP classification, S2–225 (71.8%). Table 3 demonstrates this to be the case across all states of Australia. The majority of episodes were admitted from private residence (89.5%), with 87.1% of those admitted from private residence also returning there upon completion of rehabilitation.

Table 2. Episodes submitted to the AROC database from 2004 to 2010
Impairment codes as per Table 1

Impairment code	Year							All
	2004	2005	2006	2007	2008	2009	2010	years
5.3	193	252	242	264	248	294	260	1753
5.4	479	531	579	667	636	695	615	4202
5.5	12	19	21	21	23	17	26	139
5.6	28	32	31	15	32	26	24	188
5.7	40	47	45	53	45	47	29	306
All amputee episodes	752	881	918	1020	984	1079	954	6588
All rehabilitation episodes	37 920	45 338	50 755	55 393	60 797	67 306	75 621	393 130
% amputee	2.0%	1.9%	1.8%	1.6%	1.6%	1.3%	1.3%	1.7%

Table 3. Variation in lower-limb amputee admissions (%) across impairment codes and AN-SNAP classifications by states of Australia
Impairment codes as per Table 1

	Impairment code					AN-SNAP	
	5.3	5.4	5.5	5.6	5.7	S2–224	S2–225
NSW	653 (28)	1424 (60)	58 (2)	73 (3)	150 (6)	628 (27)	1714 (73)
Vic	180 (21)	602 (72)	7 (1)	16 (2)	36 (4)	154 (18)	685 (82)
Qld	203 (32)	383 (59)	21 (3)	16 (2)	21 (3)	196 (31)	443 (69)
SA	166 (28)	379 (65)	14 (2)	10 (2)	18 (3)	165 (28)	421 (72)
Other	108 (25)	306 (71)	2 (0)	12 (3)	6 (1)	186 (45)	228 (55)

Complications and comorbidities occurring during rehabilitation were not well recorded in the dataset before 2007. In 2004, 94.7% of episodes did not record complications during rehabilitation. This figure dropped to 51.1% in 2007, and by 2010 there were only 2.7% of episodes with missing data for complications during rehabilitation. Of submitted data where complications were recorded from 2007 to 2010, 44.2% reported at least one complication, commonly being a wound infection (33.3%) or a fall (12.5%). Of submitted comorbidities data between 2007 and 2010, 67.4% had at least one comorbidity, with 43.4% having multiple comorbidities. The most commonly reported comorbidity was diabetes mellitus (43.4%). Comorbidities and complications did not vary by year or impairment code. However, analysis by AN-SNAP classification revealed that episodes in S2–225 were significantly more likely to have at least one complication (45.8%) compared with those in S2–224 (31.2%) ($\chi^2(1) = 49.9$, $P < 0.001$). Episodes in S2–225 were also significantly more likely to have multiple comorbidities (36.2%) compared with those in S2–224 (27.4%) ($\chi^2(1) = 40.6$, $P < 0.001$).

Program suspension recording changed in 2007 to enable reporting of the number of suspensions, total number of days of the suspension period, and if the suspension was planned or not. Since 2007 38.1% of episodes reported a suspension to treatment during inpatient rehabilitation. Of those, only 17.1% reported the number of suspensions, 21.1% the length, and all reported if the suspension was planned. Of those episodes with only one sus-pension (75.4%), the mean length of suspension was 4.7 days (95% CI: 3.8–5.6). The program suspension was a planned occurrence in 49.1% of episodes.

Rehabilitation outcomes

Mean LOS for all lower-limb amputee episodes was 36.1 days (95% CI: 35.4–36.9). FIM (Mot) change was 13.5 (95% CI: 13.2–13.8) and FIM (Mot) efficiency was 0.5 (95% CI: 0.5–0.5). Year-on-year analysis (see Table 4) revealed a trend for increasing LOS and FIM (Mot) change, however this did not reach significance. Table 5 provides results of rehabilitation outcomes from submitted episode data for lower-limb amputee impairment codes. *Post-hoc* analysis revealed that impairment code 5.5 had a significantly lower admission FIM (Mot) than did all other impairment codes. Impairment code 5.5 also had significantly lower discharge FIM (Mot) scores than did all other impairment codes, while impairment code 5.4 had significantly higher discharge FIM (Mot) scores than did all other impairment codes. Analysis by AN-SNAP classification revealed that LOS was longer for S2–225 at 40.6 days (95% CI: 39.8–41.5) than for S2–224 at 24.4 days (95% CI: 23.4–25.4), with a significant difference of 16.2 days (95% CI: 14.7–17.8, $P < 0.001$). FIM (Mot) differences were also found between AN-SNAP classifications, with S2–225 achieving a higher FIM (Mot) change of 16.8 (95% CI: 16.5–17.2) than the 4.8 (95% CI: 4.5–5.0) achieved for S2–224, with the mean difference of 12.0 reaching significance (95% CI: 11.5–12.6, $P < 0.001$). FIM (Mot) efficiency was also found to be different between AN-SNAP classifications, with S2–225 being 0.6 (95% CI: 0.5–0.6) compared with 0.3 (95% CI: 0.3–0.3) for S2–224, and the mean difference of 0.3 reaching significance (95% CI: 0.2–0.3, $P < 0.001$). Analysis by states (see Table 6) revealed significant variations in LOS, FIM (Mot) change and FIM (Mot) efficiency. *Post-hoc* analysis revealed NSW had shorter LOS than did either South Australia (SA) (by 3.7 days, 95% CI: 0.6–6.8, $P < 0.01$) or Victoria (Vic) (by 6.3 days, 95% CI: 3.7–9.0, $P < 0.001$), but Queensland (Qld) had significantly shorter LOS than did Vic, by 4.4 days (95% CI: 0.9–7.9, $P < 0.01$). Vic achieved a significantly greater FIM (Mot) change than did Qld, by 1.6 points (95% CI: 0.1–3.1, $P < 0.05$). FIM (Mot) efficiency was significantly greater for NSW than for SA by 0.1 (95% CI: 0.0–0.2, $P < 0.05$) and for Vic by 0.1 (95% CI: 0.0–0.1, $P < 0.05$). Caution should however be taken when considering these results due to variations in organisation of rehabilitation and prosthetic services across Australia.

Discussion

The AROC dataset proved useful for providing a snapshot of lower-limb amputee rehabilitation nationally. Since inception of the database, several modifications and improvements have been implemented to ensure that data recording is correct and accurate and provides a realistic picture of the current state of rehabilitation. For lower-limb amputees, an adjunct dataset was introduced to specifically target outcomes related to amputees. Once sufficient data has been collected, the addition of the adjunct dataset should allow a more comprehensive analysis of amputee rehabilitation. In the meantime, results from the current version of the AROC database indicate that the majority of cases were managed by the public sector, and unilateral below-knee episodes were the most common in this database, which is typically the case in amputee rehabilitation facilities.[16,17] Overall LOS can also be considered to be quite long compared with other patient populations including stroke (27 days) and orthopaedic fractures (23 days),[18,19] and amputees entering rehabilitation facilities can be considered old. The significant LOS may be attributed to several factors such as waiting for suitable wound healing to occur

Table 1. Comparison of [illegible]

LOS = length of stay.

	2004 *n* = 535	2005 *n* = 600	2006 *n* = 686	2007 *n* = 747	2008 *n* = 743	2009 *n* = 823	2010 *n* = 730	Total *n* = 4864	*p* value*
LOS (95% CI)	33.4 (31.0 35.8)—	34.2 (32.4 36.1)	35.4 (33.5 37.3)	34.8 (33.1 36.6)	34.6 (32.9 36.4)	38.1 (36.3 40.0)	39.1 (37.0 41.1)——	36.1 (35.4 36.9)—	0.0001
LOS casemix adjusted mean (95% CI)	1.0 (-3.3 1.3)—	0.1 (1.9 1.7)	0.2 (1.9 1.6)	0.1 (1.6 1.9)	0.9 (2.6 0.7)	3.1 (1.3 4.8)	3.8 (1.8 5.8)——	0.8 (0.1 1.5)—	0.0001
Admission FIM (Mot) (95% CI)	61.1 (59.8 62.5)—	61.4 (60.2 62.7)	60.3 (59.1 61.5)	61.5 (60.4 62.6)	60.8 (59.7 61.9)	59.6 (58.5 60.7)	59.1 (58.0 60.3)——	60.1 (59.7 60.6)—	0.018
Discharge FIM (Mot) (95% CI)	73.8 (72.7 75.0)—	75.1 (74.1 76.1)	73.7 (72.7 74.7)	74.9 (74.1 75.8)	73.7 (72.8 74.6)	73.6 (72.6 74.5)	74.0 (73.0 75.0)——	73.6 (73.3 74.0)—	0.101
FIM (Mot) change (95% CI)	12.7 (11.8 13.6)—	13.6 (12.8 14.5)	13.4 (12.5 14.2)	13.4 (12.6 14.2)	12.9 (12.1 13.6)	14.0 (13.2 14.7)	14.9 (14.0 15.7)——	13.5 (13.2 13.8)—	0.001
FIM (Mot) efficiency (95% CI)	0.5 (0.4 0.5)—	0.5 (0.5 0.6)	0.5 (0.4 0.5)	0.5 (0.5 0.6)	0.5 (0.4 0.5)	0.5 (0.4 0.5)	0.5 (0.5 0.5)——	0.5 (0.5 0.5)—	0.540
FIM casemix adjusted mean (95% CI)	1.5 (2.3 0.6)—	0.6 (1.4 0.3)	0.9 (1.7 -0.1)	0.6 (1.4 0.2)	1.8 (2.5 1.1)	0.5 (-1.3 0.3)	0.3 (-0.5 1.1)——	0.8 (1.1 0.5)—	0.007
Discharge to private residence *n* (%)	144 (73)	348 (81)	480 (81)	596 (84)	611 (86)	648 (83)	603 (86)	3430 (83)	0.0001
Sector: private *n* (%)	122 (23)	125 (21)	91 (13)	123 (16)	119 (16)	127 (15)	100 (14)	807 (17)	0.0001
Public *n* (%)	413 (77)	475 (79)	595 (87)	624 (84)	624 (84)	696 (85)	630 (86)	4057 (83)	

*Excluding Total in analysis.

before prosthetic casting, waiting for adequate home modifications to be made so that the amputee may safely return home, or the earlier arrival of amputees from acute setting to rehabilitation facilities.

Year-on-year analysis revealed a trend for increasing LOS, FIM (Mot) change and decreasing age. As discharge to private residence has remained relatively steady over the observation period, it appears that the lower admission FIM (Mot) scores entering rehabilitation may contribute to the longer LOS to achieve a greater FIM (Mot) change and ensure similar discharge FIM (Mot) scores. Increasing LOS inthis population appears to be contradictory to other rehabilitation patient populations who are typically experiencing decreasing rehabilitation LOS.[18,19] The decreasing age observed may be related to the increasing prevalence of diabetes mellitus in younger adults due to the increasing incidence of obesity and physical inactivity.[20–22] However several other factors may also have contributed, such as rehabilitation facilities admitting older amputees for transfer training only under reconditioning (rather than rehabilitation), or facilities not admitting older amputees from care facilities for rehabilitation as their care is already maximal.

The trend of increasing LOS and decreasing age should raise concerns within the wider amputee rehabilitation community. Clinicians and public health physicians may need to review current rehabilitation practice and pursue service delivery modifications aimed at reducing LOS and promoting good rehabilitation outcomes. To assist in the review of current reha-bilitation practice, clinicians should ensure active data collection of all items within the AROC amputee adjunct dataset, to provide a comprehensive overview of lower-limb amputee re-habilitation in Australia. Attention should be directed towards the increasing LOS to determine if improved services, such as early identification and implementation of home modifications, may assist in reducing LOS. Service delivery modifications may also need to be considered and may include earlier admittance to rehabilitation facilities to ensure rehabilitation begins as soon as possible.

Discrimination of episodes by AN-SNAP classification through use of the FIM appears to be an effective method of distinguishing functional abilities and rehabilitation outcomes of lower-limb amputees. Significant differences were found in LOS, FIM (Mot) change and efficiency between classifications. Potential exists for AN-SNAP classes to be used more effectively in planning and targeting rehabilitation programs for the lower-limb amputee population and may be a useful service-modification option to assist in the reduction of LOS. Although the FIM itself is not an amputee-specific tool, it is a widely used and useful tool for obtaining a broad snapshot of a patient's potential and allows comparison of amputees with other patient populations. AROC has recently introduced an amputee adjunct dataset which will provide more specific amputee-related rehabilitation outcomes. Although insufficient data are currently available for analysis, we believe the addition of this adjunct dataset will prove useful for investigating amputee rehabilitation nationally.

Limitations

Outcomes from this study rely upon the quality of data recorded within the database. Data within this database are recorded at

Table 5. Comparison of lower-limb amputee rehabilitation outcomes by impairment code
Impairment codes as per Table 1. LOS = length of stay, FIM = Functional Independence Measure, FIM (Mot) = motor score of the Functional Independence Measure

	5.3 *n* = 1310	5.4 *n* = 3094	5.5 *n* = 102	5.6 *n* = 127	5.7 *n* = 231	*P* value
LOS (95% CI)	35.7 (34.3–37.1)	36.3 (35.4–37.2)	39.3 (33.1–45.5)	31.3 (27.2–35.4)	37.8 (34.1–41.6)	0.110
Admission FIM (Mot) (95% CI)	59.0 (58.1–59.9)	61.2 (60.7–61.8)	49.4 (45.8–53.0)	58.5 (55.4–61.7)	56.7 (54.6–58.9)	0.0001
Discharge FIM (Mot) (95% CI)	72.4 (71.7–73.2)	74.8 (74.4–75.3)	64.6 (61.0–68.2)	70.3 (67.7–72.9)	70.1 (68.0–72.2)	0.0001
FIM (Mot) change (95% CI)	13.4 (12.8–14.0)	13.6 (13.2–14.0)	15.2 (12.8–17.7)	11.7 (9.9–13.6)	13.4 (11.7–15.0)	0.181
FIM (Mot) efficiency (95% CI)	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.6 (0.4–0.7)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.764
Discharge to private residence *n* (%)	889 (81)	2256 (85)	59 (74)	78 (79)	148 (79)	0.001
Sector: private *n* (%)	244 (19)	497 (16)	19 (19)	14 (11)	33 (14)	0.073
Public *n* (%)	1066 (81)	2597 (84)	83 (81)	113 (89)	198 (86)	

Table 6. Comparison of lower-limb amputee rehabilitation outcomes by states of Australia
NSW = New South Wales, Vic = Victoria, Qld = Queensland, SA = South Australia, LOS = length of stay, FIM = Functional Independence Measure, FIM (Mot) = motor score of the Functional Independence Measure

	NSW *n* = 2358	Vic *n* = 841	Qld *n* = 644	SA *n* = 587	Other *n* = 434	*P*-value[A]
LOS (95% CI)	34.3 (33.3–35.3)	40.7 (38.9–42.4)	36.3 (34.0–38.6)	38.1 (36.0–40.2)	34.3 (32.1–36.5)	0.0001
Admission FIM (Mot) (95% CI)	59.3 (58.6–59.9)	58.6 (57.6–59.5)	60.2 (59.0–61.4)	60.8 (59.7–62.0)	66.9 (65.6–68.2)	0.029
Discharge FIM (Mot) (95% CI)	73.0 (72.4–73.6)	73.1 (72.3–73.9)	73.1 (72.1–74.1)	74.3 (73.3–75.2)	78.3 (77.4–79.2)	0.223
FIM (Mot) change (95% CI)	13.7 (13.3–14.2)	14.5 (13.8–15.3)	12.9 (12.1–13.7)	13.4 (12.6–14.2)	11.4 (10.3–12.4)	0.036
FIM (Mot) efficiency (95% CI)	0.5 (0.5–0.6)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.4 (0.4–0.5)	0.5 (0.4–0.5)	0.002
Discharge to private residence *n* (%)	1506 (81)	642 (83)	514 (85)	422 (89)	346 (84)	0.0001
Sector: private *n* (%)	364 (15)	40 (5)	333 (52)	16 (3)	54 (12)	0.0001
Public *n* (%)	1994 (85)	801 (95)	311 (48)	571 (97)	380 (88)	

[A]Excluding 'Other' in analysis.

various rehabilitation facilities by a wide variety of clinical staff throughout Australia. To help ensure quality of data submitted to the AROC database, clinical staff undergo regular training. Data submitted to AROC are checked for validity and returned for correction if required.

Not all Australian rehabilitation facilities submit episode data to the AROC database. Currently 180 facilities submit data to AROC, and this represents more than 95% of rehabilitation facilities in Australia. However, that number has not remained constant over the observation period with the number of submit-ting facilities growing over time.

Although interesting, there are limitations in reporting outcomes by States of Australia. Whilst there were variations in rehabilitation outcomes across Australia, results also indicated variations in episodes discriminated by AN-SNAP, and impairment codes exist that may have contributed to this (see Table 3). However, there may be other factors influencing the variation in rehabilitation outcomes across Australia. These factors may include the variation in funding structures and organisations of rehabilitation and prosthetic facilities across Australia. This study is also unable to detail the variation in amputee clinical practice across Australia that would impact rehabilitation outcomes.

Finally, some amputee-specific items should be addressed to provide a clearer picture of the state of amputee rehabilitation. Although admission and discharge FIM scores are provided, information regarding level of function before amputation is lacking. Factors such as mobility before amputation are known to affect the ability of amputees to achieve successful rehabili-tation with a prosthesis.[23] Inclusion of additional outcomes may prove useful in describing rehabilitation and functional outcomes of amputees.

Conclusion

Although only a small proportion of all episodes in the AROC database, this subset of lower-limb amputee episodes has provided a useful snapshot of the current state of amputee rehabilitation in Australia. Mean age of amputees was 67.9 years with a trend for decreasing age over the observation period. Overall LOS of this amputee subset was considered high in comparison to other patient populations. However, unlike other patient populations there does not appear to be a trend for decreasing LOS. AN-SNAP classes appear effective in distinguishing rehabilitation out-comes, and could potentially be used more effectively in planning rehabilitation programs.

Competing interests

The authors of this paper declare that there are no competing interests. Brenton Hordacre receives an Australian Postgraduate Award Scholarship.

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Appendix 2

RESEARCH ARTICLE

Physiotherapy Rehabilitation for Individuals with Lower Limb Amputation: A 15-Year Clinical Series

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Abstract

Background and Purpose. Individuals with amputations are a core group in Australian rehabilitation units that have a long index length of stay. The Repatriation General Hospital (RGH) offers general rehabilitation services to the population of Southern Adelaide (a population of 350,000) and includes an on-site prosthetic manufacturing facility. Using a physiotherapy database at the RGH, we sought to answer the following questions: What are the demographic and clinical characteristics of patients admitted for lower limb prosthetic rehabilitation over 15 years? What are the times to rehabilitation outcomes? How have these changed over 15 years with changes in service delivery? **Methods.** This paper is a retrospective observational study using a physiotherapy clinical database (1996–2010) of 531 consecutive individuals with lower limb amputation at one South Australian hospital (RGH). There were two changes in service delivery: 1) a multidisciplinary interim prosthetic programme (IPP) introduced in 1998 and 2) removable rigid dressings (RRDs) introduced in 2000. Outcome measures were patient demographics, clinical characteristics and time to rehabilitation outcome markers. **Results.** Mean age was 68 years (standard deviation [SD]: 15), with 69% male, 80% dysvascular and 68% transtibial. The overall median inpatient rehabilitation length of stay (RLOS) was 39 days (interquartile range [IQR]: 26–57). Individuals with amputation entering rehabilitation each year had a higher number of co-morbidities (β: 0.08; 95% confidence interval: 0.05–0.11). Introduction of the IPP was associated with a significant reduction in time to initial prosthetic casting, independent walking and inpatient RLOS. Introduction of RRDs was associated with a significant reduction in time to wound healing, initial prosthetic casting and independent walking. **Conclusions.** Individuals with amputation were typically elderly dysvascular men with transtibial amputations. Introduction of the IPP and RRDs successfully reduced time to rehabilitation outcomes including independent walking, an outcome that is rarely reported but is of significance to patients and physiotherapists. Copyright © 2012 John Wiley & Sons, Ltd.

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Keywords

amputees; lower extremity; physical therapy (specialty); rehabilitation

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Introduction

Improvements in amputee outcomes have occurred as a result of new medical and surgical innovations. However amputation numbers remain high, and rehabilitation of individuals with amputation continues to be a core business for medical rehabilitation units across the world. Most individuals with lower limb amputation in the developed world are elderly dysvascular patients,

often presenting with diabetes mellitus (Pernot et al., 2000; Nehler et al., 2003; Stone et al., 2007). It is estimated that 700,000 Australians (3.6% of the population) were diagnosed with diabetes mellitus and that 3,394 diabetes-related lower limb amputations were performed in Australia in 2004-05 (Australian Institute of Health and Welfare, 2008).

Individuals with amputation are a core group in Australian rehabilitation units that have a long index length of stay. The long length of stay associated with the index admission is justified by clinicians as important because restoring independent mobility and community integration reduces the larger social and health service costs associated with disability. It is widely believed that growth of interventional vascular surgery has helped reduce lower limb amputation numbers in dysvascular patients (Feinglass et al., 1999; Nowygrod et al., 2006). However, it is unknown whether the demographics of individuals with amputation entering rehabilitation units now have changed. This may result in a change in the outcomes achieved, in the time taken to achieve these outcomes or in the nature of the clinical programmes provided by physiotherapists. National outcome data collected by the Australian Rehabilitation Outcomes Centre suggests that there are wide variations in physiotherapy practice across Australia, but at this stage, information on clinical practice is lacking (AROC, 2010).

Data from prosthetic rehabilitation hospital cohorts in Australia are limited. Six studies were identified (Katrak and Baggott, 1980; Hubbard, 1989; Jones, 1990; Jones et al., 1993; Lim et al., 2006; Wu et al., 2010) with all reporting demographics and clinical characteristics of the cohorts. However, only inpatient rehabilitation length of stay (RLOS) was reported as an outcome, and the identified studies failed to investigate other rehabilitation outcomes such as times to wound healing, initial prosthetic casting and independent walking. Successful wound healing is an important rehabilitation marker as it allows rehabilitation with a physiotherapist to progress towards mobilizing with a prosthesis. Reported times from amputation to initial prosthetic casting vary, ranging from 36.4 days (interquartile range [IQR]: 24–50) with soft dressings (Taylor et al., 2008) to 23.3 days (standard deviation [SD]: 19.5) with removable rigid dressings (RRDs) (Deutsch et al., 2005). A review by Van Velzen et al. (2006) reported that 56–97% of individuals with amputation regain the ability to walk; however, time to independent walking is rarely reported in the literature. Independent walking with a prosthesis remains the key outcome for a physiotherapist in an amputee rehabilitation service as it allows patients to work towards achieving independence and will likely contribute to improved quality of life (Pell et al., 1993; Hamamura et al., 2009).

The Repatriation General Hospital (RGH) offers general rehabilitation services to the population of Southern Adelaide (a population of 350,000) and includes an on-site prosthetic manufacturing facility. Individuals with lower limb amputation attend a multidisciplinary gym session with a dedicated amputee physiotherapist and prosthetist. Six sessions are conducted per week in a group setting. Sessions include upper and lower limb strengthening, prosthetic fitting and modification, balance and gait reeducation. Physiotherapy forms only part of the multidisciplinary rehabilitation service offered to individuals with amputation at the RGH. Other services are provided by rehabilitation medical consultants, rehabilitation nursing, occupational therapy (for home modifications, return to driving and return to work), social work, psychology services (if required) and dietetics (if required). During the period of observation, two significant changes in service delivery occurred. In 1998, an interim prosthetic programme (IPP) was implemented that resulted in streamlined multidisciplinary services and provided patients with an interim prosthesis that incorporated a laminated prosthetic socket with modular componentry (made by a prosthetist; Figure 1). No interim prosthesis was used prior to this, and gait retraining was achieved with an air bag system (pneumatic post-amputation mobility aid) for transtibial, knee disarticulation and transfemoral patients. Routine fitting of RRDs was introduced in 2000 (fitted by a prosthetist) for individuals with transtibial amputation (current practice dictates that individuals with transfemoral amputation are not managed with RRDs). Fitting occurred immediately post-operatively or within 24 hours. The evidence supporting RRDs indicates a reduction in oedema (Mueller, 1982; Nawijn et al., 2005), time from amputation to wound healing (Deutsch et al., 2005; Nawijn et al., 2005), time from amputation to initial prosthetic casting (Wu et al., 1979; Hughes et al., 1998; Woodburn et al., 2004; Taylor et al., 2008) and RLOS (Taylor et al., 2008).

Using a physiotherapy database of patients who received rehabilitation for a lower limb amputation between 1 January 1996 and 31 December 2010 at the RGH, we sought to answer the following questions.

Figure 1 An interim prosthesis with fully laminated prosthetic socket and modular componentry

1. What are the demographics and clinical characteristics of individuals with lower limb amputation admitted for rehabilitation and how have these changed over the observation period?
2. What are the times to rehabilitation outcomes (wound healing, initial prosthetic casting, independent walking and inpatient RLOS)?
3. How have demographics, clinical characteristics and the changing model of rehabilitation services offered at the RGH affected rehabilitation outcomes?

Method

Design

This study was a retrospective audit of a clinical physiotherapy database of consecutive individuals with lower limb amputation admitted for prosthetic rehabilitation at the RGH between 1 January 1996 and 31 December 2010. The period 1996 to 2010 marks the beginning of inpatient amputee rehabilitation at the RGH to the most recent completed year of data at the time of writing. Records were examined by two authors (B. H. and V. B.), and data were extracted for analysis. Extracted data included demographics, clinical characteristics and rehabilitation outcomes. Ethical approval was provided by the Southern Adelaide Flinders Clinical Human Research Ethics Committee.

Subjects

The RGH provides inpatient and outpatient prosthetic rehabilitation for individuals with major lower limb amputation. Amputation types included were transtibial, transfemoral, knee disarticulation, hip disarticulation, unilateral and bilateral. Acute amputation services were provided by both the RGH and hospitals that are geographically separate to the RGH.

Outcome measures

The primary rehabilitation outcome markers were wound healing, initial prosthetic casting, independent walking and inpatient RLOS. A secondary measure of total rehabilitation programme duration (RPD) was also reported. Wound healing was determined from visual inspection by the amputee physiotherapist and prosthetist and confirmed by the rehabilitation medical consultant. Independent walking was determined by the amputee physiotherapist when the patient could mobilize 10 m independently (with or without gait aid). Inpatient RLOS was defined as the time frame from when an individual with amputation was admitted to the RGH as an inpatient for prosthetic rehabilitation to discharge from the RGH. Total RPD included inpatient RLOS and rehabilitation conducted as an outpatient. 'Length of stay' in hospitals is an outcome measure that can be difficult to interpret. Whereas in some health systems it may be a surrogate for morbidity, in other systems it may represent patient preference, insurance company requirements or a lack of ambulatory alternatives (La Cour et al., 2010). In our study, we used length of stay as a surrogate for morbidity, lack of ambulatory alternatives (i.e. inability to further progress mobility of the patient), lack of discharge destination preparation (i.e. delays in home modifications) and patient preference (home or hospital-based rehabilitation). Insurance company requirements did not equally apply as a surrogate of RLOS to this data set. This is because the RGH is a publically funded hospital. Rehabilitation outcome markers were recorded in days after amputation and days after beginning rehabilitation. Information on patient demographics and clinical characteristics including age, gender, indication for amputation,

level of amputation, complications, co-morbidities and discharge destination was also collected.

Data analysis

Regression analysis was conducted to model age, total number of co-morbidities and admission numbers of individuals with amputation entering rehabilitation over the 15-year observation period. Results are reported with a regression coefficient (β) with 95% confidence interval (CI). Logistic regression analysis was used to model discharge destinations, and results are reported with an odds ratio (OR) with 95% CI. Zero truncated negative binomial regression was used to model times to wound healing, initial prosthetic casting, independent walking and inpatient RLOS. Observations from patients who did not realize a particular rehabilitation outcome were excluded from the analysis. Zero truncated negative binomial regression accounts for overdispersion and the fact that all outcomes are counts greater than zero. Results are reported as an incidence rate ratio (IRR) with 95% CI. An IRR is a ratio that describes the relative rates of experiencing an outcome given an exposure. All multivariable models were adjusted for covariates as noted in the table. Models were fitted with terms in polynomial time up to the third power as appropriate to explain variation over the period of the study. A p-value of 0.05 (two-tailed) was considered statistically significant. All analyses were performed using Stata 11.2 for Windows (StataCorp, 2009).

Results

Outcome of patients through rehabilitation

A total of 531 consecutive individuals with amputation were admitted for prosthetic rehabilitation at the RGH between 1996 and 2010. Figure 2 presents the flow of patients through to the completion of rehabilitation. No significant difference was found in admission numbers per year over the observation period (β: 0.63; 95% CI: −0.34 to 1.61).

Patient demographics and clinical characteristics

Table 1 summarizes patient demographics and clinical characteristics. Results indicate that age significantly decreased across the observation period (β: 0.49; 95% CI: 0.20–0.79) whereas the total number of co-morbidities increased across the observation period (β: 0.08; 95% CI: 0.05–0.11; Table 2). The number of individuals with amputation discharged home also decreased across the observation period (OR: 0.92; 95% CI: 0.86–0.99; Table 2). From 1996 to 2003, eight patients were re-admitted to hospitals, whereas from 2004 to 2010, 41 patients were re-admitted to hospitals.

Rehabilitation outcomes

Figure 2 presents results of rehabilitation outcomes of the 531 patients admitted for prosthetic rehabilitation at the RGH. Time to rehabilitation outcomes at the beginning (1996) and end (2010) of the observation period are presented in Table 3.

Effect of demographics, clinical characteristics and the changing model of rehabilitation services on rehabilitation outcomes

Results for the rehabilitation outcomes wound healing, initial prosthetic casting, independent walking and inpatient RLOS are presented in Figures 3 and 4. Multivariable predictors of times to wound healing, initial prosthetic casting, independent walking and inpatient RLOS are summarized in Table 4. The introduction of the IPP was associated with a significant reduction in time to cast (IRR: 0.64; 95% CI: 0.56–0.72), independent walking (IRR: 0.80; 95% CI: 0.73–0.87) and inpatient RLOS (IRR: 0.49; 95% CI: 0.30–0.79). Introduction of RRDs (applied to transtibial amputees only) was associated with a significant reduction in time to wound healing (IRR: 0.33; 95% CI: 0.27–0.40), prosthetic casting (IRR: 0.65; 95% CI: 0.57–0.73) and independent walking (IRR: 0.87; 95% CI: 0.76–1.00).

Discussion

The aim of the present study was to describe changes in the demographics and clinical characteristics of individuals with lower limb amputation admitted to a Southern Adelaide area hospital for rehabilitation and to determine how changes in these characteristics and service delivery over the period of observation have affected rehabilitation outcomes in the patient population. From these findings, we intend to discuss the broader significance to physiotherapists working with individuals with lower limb amputations.

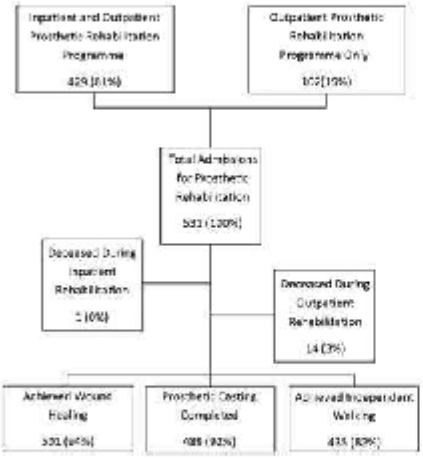

Figure 2 Outcome of cohort of individuals with lower limb amputation admitted for rehabilitation at the Repatriation General Hospital between 1996 and 2010

Patient demographics and clinical characteristics

Age, gender and indication for amputation of this cohort are similar to that reported by other recent Australian and international amputee rehabilitation cohorts (Rommers et al., 1996; Kazmers et al., 2000; Toursarkissian et al., 2002; Cruz et al., 2003; Nehler et al., 2003; Aulivola et al., 2004; Lim et al., 2006; Wu et al., 2010). A higher percentage of transtibial amputees were admitted to the RGH (68%) compared with previous published data (44–59%), whereas a lower percentage of individuals with transfemoral amputation (22%) were seen compared with earlier data (26–55%; Katrak and Baggott, 1980; Hubbard, 1989; Jones et al., 1993; Kazmers et al., 2000; Nehler et al., 2003; Lim et al., 2006). However, comparison with a more recent Australian cohort covering a similar observation period (1994–2006) reveals a similar percentage of transtibial amputees admitted for rehabilitation (66%; Wu et al., 2010). We believe that the reported differences compared with historical published data are a reflection of the predominantly dysvascular nature of individuals with amputation admitted to the RGH, advances and improvements in limb salvage surgery, diabetic care, foot care and wound management, which have occurred in recent years.

Table 1. Mean (SD) or *n* (%) of patient demographics and clinical characteristics

Clinical characteristics	Participants (*n* = 531)
Age (years)	68 (SD: 15)
Gender	
Male	367 (69%)
Female	164 (31%)
Indication	426 (80%)
Dysvascular	250 (59%)
Dysvascular with diabetes	44 (8%)
Trauma	15 (3%)
Tumour	22 (4%)
Infection	24 (5%)
Other	
Type	
Transtibial	361 (68%)
Transfemoral	116 (22%)
Knee disarticulation	4 (1%)
Hip disarticulation	6 (1%)
Bilateral transtibial	29 (5%)
Bilateral transfemoral	3 (1%)
Bilateral transtibial/transfemoral	12 (2%)
Discharge destination	
Home	327 (76%)
Transitional care	19 (4%)
Hospital	49 (11%)
Hostel	21 (5%)
Nursing home	12 (3%)
Deceased	1 (0%)
Co-morbidities	
Peripheral vascular disease	329 (62%)
Diabetes mellitus	261 (49%)
Interstitial heart disease	163 (31%)
Osteoarthritis	43 (8%)
Hypertension	143 (27%)
Chronic renal failure	52 (10%)
Previous amputation	49 (9%)

Across the observation period there was a decrease in the number of individuals with lower limb amputation discharged home despite the average age of patients decreasing significantly. We believe that one of the major reasons for this trend was the increasing number of co-morbidities observed in this population, which meant that overall patients were frailer and less appropriate for discharge home. One of the most common co-morbidities in this population was type 2 diabetes mellitus. It is known that the incidence of type 2 diabetes mellitus is increasing worldwide, primarily because of increasing prevalence of obesity and physical inactivity (Wild et al., 2004; Eckel et al., 2005; Hu, 2011). Clinicians, including physiotherapists, may need to consider the implementation of chronic disease self-management approaches to promote changes

Table 2. Number of admissions, mean (SD) age of patients, mean (SD) number of co-morbidities and discharge home (%) for each year of observation

Year	Admissions (*n*)	Age (years)	Co-morbidities (*n*)	Discharge home (%)
1996	38	69.7 (13.1)	2.3 (1.0)	81
1997	25	70.2 (9.5)	2.5 (1.4)	77
1998	21	70.7 (14.5)	2.2 (1.4)	91
1999	35	73.6 (10.5)	2.8 (1.3)	92
2000	33	70.4 (13.1)	2.5 (1.2)	79
2001	35	71.1 (13.9)	3.0 (1.8)	65
2002	26	73.0 (11.7)	3.0 (1.6)	88
2003	49	67.6 (17.3)	3.4 (1.8)	80
2004	49	66.6 (19.1)	2.9 (1.6)	69
2005	35	67.2 (17.2)	3.3 (1.7)	80
2006	43	68.9 (12.6)	3.2 (1.8)	71
2007	33	66.2 (16.1)	3.5 (1.9)	67
2008	37	64.4 (12.9)	3.4 (2.0)	77
2009	36	65.8 (16.5)	3.4 (1.8)	64
2010	36	65.1 (13.9)	3.3 (1.7)	91

leading to more healthy lifestyles amongst the amputee population (Tuomilehto et al., 2001; Heideman et al., 2011; Hu, 2011).

Rehabilitation outcomes

Identifying improvements in the amputee rehabilitation service relied upon identifying important clinical outcomes and measuring them as changes were made to the service during the period of observation. Four primary outcomes were used in this study to monitor patient rehabilitation — wound healing, initial prosthetic casting, independent walking and inpatient RLOS. Wound healing and time to first prosthetic casting are traditional milestones in amputee rehabilitation as early successful wound healing allows progression to further rehabilitation, including mobility with a prosthesis. The initial aim of clinicians, practitioners and medical staff is to promote wound healing because early successful wound healing is often immediately followed by prosthetic casting (Nawijn et al., 2005), as was demonstrated by the present data. We found that time from amputation to first prosthetic casting was similar to time frames reported in previous studies (Deutsch et al., 2005; Taylor et al., 2008). The initial casting for a prosthetic socket will lead to the use of an interim prosthesis and a more intensive phase of rehabilitation with the ultimate goal being to achieve independent walking.

In contrast, the time taken to achieve independent walking, which is a key rehabilitation goal for individuals with lower limb amputation and amputee physiotherapists, is not well reported in the literature. The ability to walk independently was achieved by a high percentage of patients (83%) in this study. This is well within the range (56–97%) reported by Van Velzen et al. (2006). However, there was more variation in the time taken to achieve independent walking in the current data owing to changes in service delivery over the observation period. We believe that reporting on time to independent walking should be included as a key measure in amputee rehabilitation studies to inform improvements in physiotherapy service delivery.

Effect of service delivery changes on rehabilitation outcomes

Interim prosthetic programmes vary across rehabilitation sites. Only one previous study comparing a public and private IPP model could be found but did not report on outcomes used in this study (Gordon et al., 2010). During the period of observation, the

Table 3. Median (IQR) for rehabilitation outcomes in days after amputation and days after beginning rehabilitation

	Days post-amputation			Days of rehabilitation		
Year (admissions)	1996 (38)	2010 (36)	All (531)	1996 (38)	2010 (36)	All (531)
Outcome marker						
Start physiotherapy	46 (36–70)	14.5 (8–27)	15 (9–38)	N/A	N/A	N/A
Wound healing	51 (36–79)	25 (21–35)	27 (22–54)	1 (1–1)	11 (1–14)	10 (1–17)
Prosthetic casting	62.5 (44–80)	34 (27–62)	31.5 (24–60)	9 (4–20)	22 (15–28)	14 (8–22)
Independent walking	105 (66–150)	61 (43–93)	68 (48–110)	30 (22–78)	47 (31–77)	45 (29–71)
Inpatient RLOS	N/A	N/A	N/A	34.5 (21.5–48.5)	43 (33–57)	39 (26–57)
Total RPD	147.5 (111–225)	124 (70–154)	133 (93–198)	84 (57–136)	103.5(58–135)	106 (65–155)

N/A = not applicable; RLOS = rehabilitation length of stay; RPD = rehabilitation programme duration.

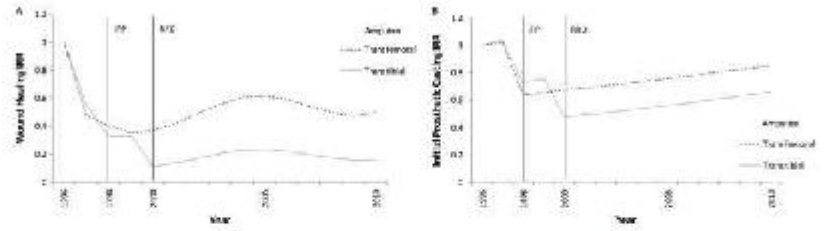

Figure 3 Change in incidence rate ratio (IRR) across the observation period for (A) time to wound healing and (B) time to initial prosthetic casting for individuals with transtibial and transfemoral amputation of any age or indication for amputation with no co-morbidities or complications. IPP = interim prosthetic programme; RRD = removable rigid dressing

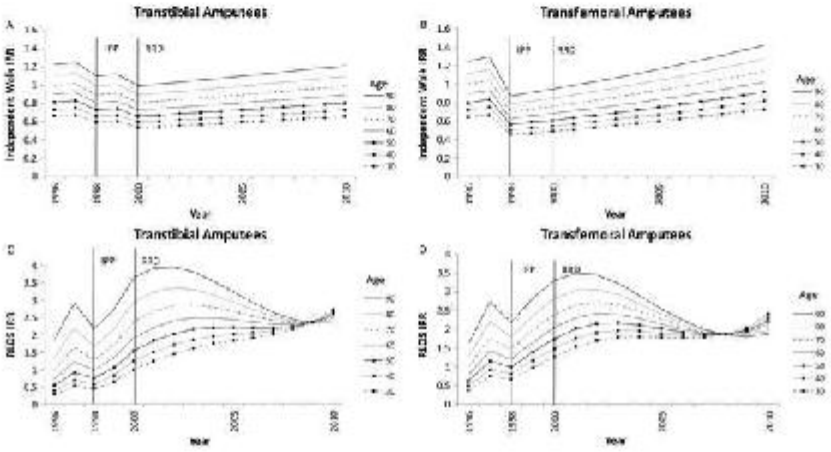

Figure 4 Change in incidence rate ratio (IRR) across the observation period for time to independent walking for individuals with (A) transtibial and (B) transfemoral amputation and inpatient rehabilitation length of stay (RLOS) for individuals with (C) transtibial and (D) transfemoral amputation, based on age, with any indication for amputation, no co-morbidities or complications. IPP = interim prosthetic programme; RRD = removable rigid dressing

introduction of the IPP was associated with a significant reduction in the time taken to achieve initial prosthetic casting, independent walking and inpatient RLOS, suggesting that it is a valuable part of a service model. The reduction in time to initial prosthetic casting was not unexpected as the programme supplied patients with an interim prosthesis that was not done previously. However, the reduction in time to independent walking has not been reported previously and is an important milestone for the patient in regaining independence (Pell et al., 1993; Hamamura et al., 2009). We believe that the reduction is primarily due to the IPP providing access to an interim prosthesis (Figure 1), enabling individuals with lower limb amputation to practice more appropriate patterns of weight shifting, stepping and walking with a physiotherapist sooner in the rehabilitation phase. Physiotherapists working with individuals with lower limb amputations are encouraged to initiate service modifications, such as an IPP if one is not already in place, which facilitate mobility retraining as soon as possible in the rehabilitation process.

The use of RRDs with individuals with transtibial amputation should now be common practice in many services across the developed world. The introduction of RRDs occurred in 2000 at the RGH and was

Table 4. Predictors of rehabilitation outcome measures

	Wound healing	Initial prosthetic casting	Independent walking	Inpatient RLOS
	Multivariable IRR (95% CI)			
Time				
1996 (ref)	1.00	1.00	1.00	1.00
2002	0.39 (0.12, 1.31)	1.15 (0.98, 1.36)	1.19 (1.11, 1.27)***	5.03 (2.22, 11.41)***
2010	0.39 (0.12, 1.31)	1.40 (0.96, 2.03)	1.50 (1.13, 1.87)***	4.46 (2.06, 9.68)***
IPP[a]	1.22 (0.69, 2.17)	0.64 (0.56, 0.72)***	0.80 (0.73, 0.87)**	0.49 (0.30, 0.79)**
RRD[b]	0.33 (0.27, 0.40)***	0.65 (0.57, 0.73)***	0.87 (0.76, 1.00)*	1.15 (0.97, 1.36)
Age	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.01 (1.01, 1.02)***	—
1996	—	—	—	1.03 (1.02, 1.04)***
2002	—	—	—	1.02 (1.01, 1.02)***
2010	—	—	—	1.00 (0.99, 1.00)
Gender				
Male (ref)	1.00	1.00	1.00	1.00
Female	1.18 (1.03, 1.36)*	1.07 (1.00, 1.15)	1.07 (0.99, 1.16)	1.06 (0.94, 1.19)
Amputation type				
Transtibial (ref)	1.00	1.00	1.00	1.00
Transfemoral	0.68 (0.56, 0.82)***	1.06 (0.86, 1.26)	1.16 (1.07, 1.27)***	0.85 (0.75, 0.97)*
Bilateral	0.96 (0.75, 1.23)	1.13 (1.00, 1.27)	1.33 (1.17, 1.50)***	1.16 (0.95, 1.41)
Cause				
Dysvascular (ref)	1.00	1.00	1.00	1.00
Dysvascular DM	0.95 (0.63, 1.43)	1.01 (0.82, 1.25)	0.96 (0.77, 1.18)	0.95 (0.67, 1.34)
Trauma	0.83 (0.61, 1.14)	0.90 (0.76, 1.07)	0.94 (0.79, 1.11)	0.99 (0.75, 1.31)
Tumour	1.02 (0.62, 1.66)	0.85 (0.65, 1.11)	1.07 (0.84, 1.40)	1.11 (0.73, 1.70)
Infection	0.69 (0.48, 1.00)	0.74 (0.60, 0.93)*	1.04 (0.84, 1.29)	0.87 (0.65, 1.17)
Other	0.88 (0.62, 1.26)	0.76 (0.60, 0.95)*	1.07 (0.88, 1.29)	0.94 (0.71, 1.26)
Co-morbidities				
IHD	0.71 (0.57, 0.89)**	0.99 (0.91, 1.07)	1.04 (0.96, 1.14)	0.94 (0.82, 1.07)
PVD	0.96 (0.81, 1.14)	0.99 (0.90, 1.08)	0.96 (0.87, 1.06)	0.93 (0.79, 1.08)
DM	0.96 (0.65, 1.41)	0.82 (0.67, 1.01)	1.04 (0.86, 1.27)	1.00 (0.74, 1.36)
Complications				
Wound breakdown	1.59 (1.30, 1.93)***	1.26 (1.05, 1.52)	1.17 (1.02, 1.33)*	1.31 (1.11, 1.54)**
Transtibial	—	—	1.14 (1.00, 1.31)	—
Transfemoral	—	—	1.47 (1.24, 1.76)***	—
Bilateral	—	—	1.90 (1.39, 2.60)***	—
Other illness	0.91 (0.70, 1.17)	1.10 (1.00, 1.20)*	1.30 (1.17, 1.43)***	1.19 (1.01, 1.41)*
Stump skin problem	0.89 (0.73, 1.09)	0.97 (0.87, 1.07)	1.21 (1.09, 1.35)***	1.01 (0.85, 1.20)
Fall	1.20 (0.74, 1.95)	0.99 (0.86, 1.14)	1.08 (0.93, 1.26)	—
40 years old	—	—		2.33 (1.23, 4.41)**
65 years old	—	—		1.35 (1.06, 1.71)*
90 years old	—	—		0.93 (0.64, 1.37)
Medically unstable	0.74 (0.39, 1.45)	0.93 (0.64, 1.34)	1.40 (0.70, 2.80)	1.63 (0.63, 4.22)
Problem: other foot	0.89 (0.69, 1.13)	1.02 (0.90, 1.15)	1.21 (1.05, 1.39)	—
1996	—	—	—	0.58 (0.36, 0.94)*
2002	—	—	—	0.85 (0.66, 1.10)
2010	—	—		1.42 (1.01, 1.99)
Stump pain	—	—	0.87 (0.64, 1.17)	1.21 (0.77, 1.92)

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

[a]Interim prosthetic programme (IPP) was introduced in 1998.

[b]Removable rigid dressing (RRD) was introduced in 2000.

Each variable was adjusted for all other co-variables in the table. RLOS = rehabilitation length of stay; IRR = incidence rate ratio; CI = confidence interval; DM = diabetes mellitus; IHD = interstitial heart disease; PVD = peripheral vascular disease.

associated with a significant reduction in time from amputation to wound healing, initial prosthetic casting and independent walking for individuals with transtibial amputation. These findings are consistent with previous evidence that has demonstrated that RRDs reduce time to wound healing (Deutsch et al., 2005; Nawijn et al., 2005), time to initial prosthetic casting (Wu et al., 1979; Hughes et al., 1998; Woodburn et al., 2004; Taylor et al., 2008) and RLOS (Taylor et al., 2008). However, this study provides some of the first evidence to suggest that their use is associated with a reduction in the time taken to achieve independent walking. This is a key finding for physiotherapists as they are often primarily concerned with restoring the mobility of their patients. In consultation with treating physiotherapists and prosthetists, amputee rehabilitation services should ensure that individuals with transtibial amputation are provided with RRDs following limb amputation in accordance with best practice guidelines.

Despite the introduction of the IPP and RRDs, it is interesting to note that times to initial prosthetic casting, independent walking and inpatient RLOS based on IRRs are increasing towards the end of the observation period (Figures 3 and 4). We speculate that these increases may be due to the earlier stage in acute recovery at which individuals with lower limb amputation are admitted to rehabilitation from acute hospital services. Whilst this process may reduce acute hospital length of stay, it may impact negatively on RLOS. However, this may be countered by the benefit of earlier exposure to physiotherapy rehabilitation services. These changes may also be due to the increase in a more co-morbid population that is admitted for rehabilitation and indicate the need for an amputee rehabilitation service better tailored for this population. Further investigation is required into the increasing time to rehabilitation outcomes and how service provision can be improved to address these trends.

Limitations

Our study was based at a single institution, and there are likely to be differences in admission criteria and services provided to patients; therefore, results may not be generalizable to other amputee rehabilitation facilities. Further limitations of this study include the retrospective nature of the analysis, which relied upon the quality of documentation and recording in the physiotherapy clinical database and medical notes. Not all desirable data were available to undertake a complete and thorough analysis of the outcomes of the amputee rehabilitation service. For example, information regarding residual limb (stump) length, surgical technique, prosthetic equipment and premorbid mobility are all factors that were not documented in this study but are likely to influence amputee rehabilitation outcomes. Finally, no follow-up of function in the community was conducted to determine the long-term outcomes from the amputee rehabilitation.

Summary

In the present cohort, individuals with lower limb amputation were typically elderly dysvascular men with transtibial amputations. Introduction of the IPP and RRDs successfully reduced time to all primary rehabilitation outcomes including time to wound healing, initial prosthetic casting, independent walking and inpatient RLOS.

Implications

Three implications relevant for amputee physiotherapists and clinicians can be drawn from this study. First, we believe that time to independent walking is an outcome of value, which should be tracked by physiotherapists. For the present cohort, it has proven a useful outcome in assessing the effectiveness of service modifications during the period of observation. Second, physiotherapists need to consider service modifications that would enable individuals to undertake mobility retraining earlier in their rehabilitation to reduce time to rehabilitation milestones. Third, in light of the changing characteristics of individuals with lower limb amputation now presenting for rehabilitation described in this study, it is likely that physiotherapists, and clinicians in general, will need to tailor services to target this younger more co-morbid population.

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Appendix 3

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Article

Use of an Activity Monitor and GPS Device to Assess Community Activity and Participation in Transtibial Amputees

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Abstract: This study characterized measures of community activity and participation of transtibial amputees based on combined data from separate accelerometer and GPS devices. The relationship between community activity and participation and standard clinical measures was assessed. Forty-seven participants were recruited (78% male, mean age 60.5 years). Participants wore the accelerometer and GPS devices for seven consecutive days. Data were linked to assess community activity (community based step counts) and community participation (number of community visits). Community activity and participation were compared across amputee *K*-level groups. Forty-six participants completed the study. On average each participant completed 16,645 (standard deviation (SD) 13,274) community steps and 16 (SD 10.9) community visits over seven days. There were differences between *K*-level groups for measures of community activity ($F_{(2,45)} = 9.4$, $p < 0.001$) and participation ($F_{(2,45)} = 6.9$, $p = 0.002$) with lower functioning K1/2 amputees demonstrating lower levels of community activity and participation than K3 and K4 amputees. There was no significant difference between K3 and K4 for community activity ($p = 0.28$) or participation ($p = 0.43$). This study demonstrated methodology to link accelerometer and GPS data to assess community activity and participation in a group of transtibial amputees. Differences in *K*-levels do not appear to accurately reflect actual community activity or participation in higher functioning transtibial amputees.

Keywords: amputees; rehabilitation; technology; activity monitor; activity; participation; wearable sensors

1. Introduction

Successful reintegration into the community following lower-limb amputation is a key aim of both rehabilitation clinicians and patients [1–4]. Community integration may be characterized by the domains of activity and participation as outlined in the International Classification of Functioning, Disability and Health (ICF) [5]. Prosthetic mobility is an activity which has been associated with improved quality of life [6], greater involvement in social activities [6,7] and activities of daily living [8,9], and is important for participation in employment and recreational roles [10]. Following amputation only 26%–62% of patients achieve outdoor mobility [11] limiting the capacity to participate in the community. For clinicians and researchers, assessment of community activity and participation following rehabilitation is a key marker of successful prosthetic rehabilitation and intervention effectiveness. Therefore there is a need to accurately quantify these domains.

Typically, the domains of activity and participation are assessed using either subjective or objective measures. Subjective measures, such as the Locomotor Capabilities Index [12] and activity diaries, have been shown to be unreliable and overestimate activity in lower-limb amputees [13,14]. Conversely, performance on objective clinical assessments have shown moderate to strong correlations with community based activity measures [15], and may be representative of the capacity to perform that activity in the community. Objective measures of ambulatory function are used by clinicians to guide prosthetic prescription and assess outcomes from rehabilitation. These measures include the amputee mobility predictor (AMP-PRO) [16], and timed walking tests of gait velocity (*i.e.*, 10 m walk test) and endurance (*i.e.*, 6 min walk test). Briefly, the AMP-PRO assesses a range of functional activities providing a score which assists in classifying amputee *K*-levels (K0, K1, K2, K3, K4) and guiding prosthetic prescription [17]. Higher *K*-levels (e.g., K4) indicate amputees with potential for greater functional ability, who may benefit from more advanced prosthetic componentry [16]. In addition to the AMP-PRO, clinically assessed timed walking tests of gait velocity and endurance are often used by clinicians. These tests are associated with community activity and represent complementary measures to further interpret community activity and participation potential [15,18–20]. However, a limitation of clinical assessments is that they fail to replicate the range of physical demands and unpredictable nature of community ambulation and participation, and as such, these measures may not accurately reflect actual levels of community activity and participation [1].

With recent advances in wearable technology [21], accelerometer-based monitoring devices to assess step-counts and global positioning satellite (GPS) devices to assess location offer the ability to obtain accurate objective measures of community activity and participation [21–26]. Activity data derived from accelerometer devices has been successfully collected in amputees previously [13,15,27], but, by its nature, does not provide information about the location in the community where the activity occurs. The addition of GPS data provides a means of mapping position in the community, but introduces challenges for ensuring reliable data capture and synchronisation with activity data [28]. Recently, GPS and step count data were collected in a transfemoral amputee case study, demonstrating potential to provide accurate information for clinicians [29]. However, it is currently unknown if separate accelerometer and GPS data can be captured simultaneously and successfully linked in order to assess community activity and participation in a larger cohort of transtibial amputees. Additionally, we are unaware of any studies which have used separate wearable technology devices to determine if

differences do exist for community activity and participation between amputee *K*-levels. We believe it is important for the field of amputee rehabilitation to further investigate the use of wearable technology to assess community activity and participation, and determine the nature of relationships between community and clinic based measures.

Aims/Hypothesis

The primary aim of this study was to assess the ability to use wearable technology (accelerometer-based monitoring devices to assess step-counts and GPS devices) to measure community activity and participation in rehabilitated transtibial amputees. The secondary aim was to determine if community activity and participation was different for predicted *K*-levels as assessed by AMP-PRO and timed mobility measures. We hypothesised that the combination of accelerometer and GPS data to assess community activity and participation would be feasible and that community based measures would differ between amputee *K*-levels.

2. Methods

2.1. Participants

Forty seven rehabilitated unilateral transtibial amputees were recruited. All participants had been correctly fitted with a definitive prosthesis at least six months prior to testing, and correct prosthetic fit and comfort were confirmed with the participant and their prosthetist prior to inclusion in the study. Participants were eligible if they achieved prosthetic mobility. Amputees not provided with a prosthesis for mobility (functional level K0) were excluded. The majority of recruited participants were male (79%), with a mean age of 59.7 (range 19–98) years and were 16.2 (standard deviation (SD) 18.9) years since amputation. Primary indications for amputation were trauma (38%) or peripheral vascular disease (38%). Ethical approval was provided by the Southern Adelaide Clinical Human Research ethics committee and all participants provided written informed consent in accordance with the Declaration of Helsinki.

2.2. Equipment

2.2.1. Step Activity Monitor

A StepWatch3 Activity Monitor (SAM) (Cyma Corp, Seattle, WA, USA) was fitted to each participant's prosthesis in accordance with manufacturer's recommendations. The SAM is an accelerometer and microprocessor based activity monitor measuring 6.5 cm × 5.0 cm × 1.5 cm verified for use in people with lower-limb amputations [30]. The SAM was set to record stride count data for each minute of programmed use [15]. Step count data was obtained by multiplying the stride count by two. Data from the SAM was downloaded using StepWatch software (version 3.1b), and stored within the software database.

2.2.2. Global Positioning System

A QStarz BT-Q1000XT (Qstarz International Co., Ltd., Taipei, Taiwan) 66-channel tracking global positioning system (GPS) travel recorder was used to record latitude, longitude, local date and time of each participant's position for every five seconds of programmed use. The device measures 7.2 cm ×4.7 cm ×2.0 cm, has a battery life of 42 h and accuracy error of less than three metres. Data from the GPS unit were imported to QTravel software (version 1.46) and stored within the software database.

Figure 1. The SAM and GPS devices attached to a prosthesis for data collection. The SAM was positioned according to the manufacturers' recommendations. The GPS was attached to the same strap as the SAM device for convenience.

2.3. Procedure

Participants were supplied with SAM and GPS devices. Both devices were secured to the participant's prosthesis with a single Velcro strap (see Figure 1). The devices remained attached to the prosthesis for the duration of the study period. The SAM and GPS devices were programmed for data collection using separate networked computers, thereby ensuring local time for each device was identical and preventing mismatched times in the data linkage process. Participants wore the SAM and GPS devices for a period of seven consecutive days and were supplied with a battery charger and clear written instructions for charging the GPS device nightly [31]. At the time of provision of SAM and GPS devices, clinical characteristics (age, time since amputation and indication for amputation), employment status and standard clinical measures were collected. These standard clinical measures were the AMP-PRO, gait velocity, and gait endurance assessed by the six minute walk test (6MWT). *K*-levels were assigned by an experienced physiotherapist during assessment of standard clinical measures and clinical characteristics, primarily using the AMP-PRO to guide classification [16]. Briefly, K1 are limited or unlimited household ambulators, K2 are limited community ambulators, K3 are community ambulators capable of traversing most environmental barriers, and K4 amputees are capable of high impact, stress or energy levels [16]. Assessment of gait velocity and the 6MWT were selected based on their previous use in lower-limb amputees [16,18,19]. Gait velocity was assessed

using an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA) with embedded pressure sensors to capture individual footfall data over an active area of 4.9 m × 0.6 m. Participants completed 10 consecutive walking trials over the GAITRite at their self-selected gait speed. Data were collected at 120 Hz and analysed using GAITRite software (version 4.5). The 6MWT [32] was used to assess endurance and was assessed over a 20 m track with the participant turning at each end.

2.4. Data Analysis

2.4.1. Data Linkage

Datasets obtained from the SAM and GPS devices were exported as comma-separated value (CSV) files from the respective software for each device. Within Microsoft Excel (2010) both SAM and GPS datasets were ordered chronologically and trimmed to ensure each dataset contained only seven consecutive complete periods of 24 h. As the SAM data was recorded per minute and the GPS per five seconds, local time of recorded data for both the SAM and GPS was trimmed to hour and minute values only so that the two sets of time values were identical. Local time for each dataset was converted to a time value ranging from 0 to 0.99930556, representing unique time values from 00:00 to 23:59. In a similar manner local date was converted to a date value represented as an integer for dates ranging from 1 January 1900 to 31 December 9999. A variable coded as Time_Date was generated in both datasets as a unique local time and date identifier and was calculated as the addition of the time value and date value. Latitude and longitude data obtained from the GPS was linked to step count data using Microsoft Excel's ―lookup‖ function to link the unique Time_Date variable created. Similar use of date and time stamps has been reported in previous studies to link data from various forms of wearable technology [33,34]. As a result of reducing GPS local time data to hour and minute values, up to 12 GPS latitude and longitude values were available for each minute of recorded data, and in this instance, the first latitude and longitude data values were used to link to the SAM dataset. The final linked dataset therefore contained step count and GPS latitude and longitude data for each minute of the seven consecutive days of data collection. Community visits were defined as events where the participant left their home and attended a location in the community [5]. Individual community visits were analysed by recounting latitude and longitude data for the assessed seven consecutive day period in chronological order within QTravel (version 1.46). QTravel incorporates Google Maps and Google Earth software which utilises satellite imagery to provide geographic information. Community visit events were visually identified from this geographic information. These events were then manually coded as one of seven community participation categories external to the participants home (see Box 1 for a description of categories). If required verbal confirmation was obtained from participants ensuring accurate identification of community participation. Community participation, defined as involvement in life situations [5], was assessed as the total number of individual visits to these categories. Community activity was assessed as the total step count out of home and was calculated as the sum of step counts across the seven community participation categories [5,35].

Box 1. The seven community categories with examples which were used to assess community activity and participation in rehabilitated transtibial amputees.

Community Participation Categories

Category	**Examples**
Employment	Paid employment activities
Residential	Housing other than own home
Commercial	Shopping centres, local shops
Health services	Hospital, general practitioner, physiotherapist, chiropractor, pharmacist
Recreational	Oval, sports, beach, walk in community
Social	Restaurant, café, hotel, cinema

2.4.2. Statistical Analysis

The normality of data was checked with a Shapiro-Wilk normality test and where required data transformations were performed to achieve normality. To assess completeness and quality of GPS data we assessed missing GPS data points (%) prior to linkage, and missing step count data (%) in the linked dataset. Missing GPS data were assessed by comparing the expected number of cells with recorded data (n = 120,960) to observed number of cells with recorded data. Missing step count data from the linked datasets were analysed as the difference between step counts linked to GPS data and total step counts from the SAM. Descriptive statistics were used to characterise community activity based step counts and community participation visit data for each of the community participation categories. Amputee *K*-levels were analysed as three separate groups due to the low number of recruited amputees in the K1 and K2 categories. The categories were K1/2, K3, and K4. Clinical characteristics of age and time since amputation were analysed between *K*-level groups using separate one-way ANOVA's. Employment status and indication for amputation (peripheral vascular disease (PVD), trauma, other) were analysed between *K*-level groups with a Chi-Square test. Separate one-way ANOVA's were used to determine if there were differences in community based step counts, community visits, gait velocity, and the 6MWT. Post-hoc analyses were performed for ANOVA analyses with significant results using Bonferroni adjustment. Pearson correlation was used to assess the association between total step count from the accelerometer data alone and our measure of community activity and participation to determine if an accelerometer alone could be used as a simple assessment of community activity and participation. Significance level was set at $p \leq 0.05$ and SPSS software was used for all statistical analyses (IBM corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0).

3. Results

A total of 47 transtibial amputees were recruited to participate in the study. One was excluded due incomplete GPS data resulting from failure to charge the GPS battery as instructed. For the remaining

46 datasets, 6.5% (SD 7.3%) of GPS data was unavailable due to lost signal. As a result of incomplete GPS data due to signal loss, 5.3% (SD 5.9%) of all steps recorded by the SAM were not linked to GPS positional data. For our measures of community activity and participation, amputees completed on average 16,645 (SD 13,274) steps in the community and visited 16.4 (SD 10.9) community facilities over a consecutive seven day period. A summary of activity and participation measures is provided in Table 1.

Table 1. A summary of community activity and participation for each participation category.

Activity	Step Count Mean (SD) per Week	Community Visit Mean (SD) per Week
Employment	5,323 (11,873)	3.4(8.4)
Residential	2,603(3,165)	2.9(2.8)
Commercial	3,909(4,102)	5.2(3.7)
Health Service	776 (1,280)	1.1(1.4)
Recreational	1,950(3,604)	1.0(1.5)
Social	1,733(3,512)	1.9(1.7)
Other	350(723)	0.8(1.5)
Home	25,285(14,366)	-
Lost in linkage	2,353(3,077)	-
Unidentified	222(612)	-
Total	44,504(22,600)	16.4(10.9)

Lost in linkage = step count data that was recorded on the SAM while there was inadequate satellite signal for the GPS device; Unidentified = step count data that was unable to be categorised as one of the seven community participation categories, or home.

Clinical characteristics (age, time since amputation and indication for amputation) and employment status were analysed for *K*-level categories. There were significant differences between *K*-level categories for age ($F_{(2,43)} = 4.2$, $p = 0.022$), but there was no significant difference for time since amputation ($p = 0.104$), indication for amputation ($p = 0.112$) or employment status ($p = 0.077$). Post-hoc analysis revealed K1/2 amputees were older than K4 amputees (95%CI 4.8–29.9, $p = 0.008$). There was no significant difference in age between K1/2 and K3 amputees ($p = 0.098$), or between K3 and K4 amputees ($p = 0.171$) (see Table 2).

There were differences between *K*-level groups for our defined measures of community activity ($F_{(2,43)} = 9.4$, $p < 0.001$) and community participation ($F_{(2,43)} = 6.9$, $p = 0.002$). As expected, post-hoc analysis revealed K1/2 amputees completed significantly less community steps than K3 amputees (95%CI 8.2–128.3, $p = 0.021$) and K4 amputees (95%CI 39.2–150.0, $p < 0.001$). However, there was no significant difference in the number of community steps between K3 amputees and K4 amputees ($p = 0.283$). For community participation, post-hoc analysis revealed K1/2 amputees were involved in significantly less community visits than K3 amputees (95%CI 0.01–0.64, $p = 0.049$) and K4 amputees (95%CI 0.14–0.74, $p = 0.002$). However, there was no significant difference in the number of community visits undertaken by K3 and K4 amputees ($p = 0.431$).

Table 2. Clinical characteristics for *K*-level categories.

	K1/2 (*n* = 5)	K3 (*n* = 13)	K4 (*n* = 28)	Statistic
Age (years), mean (SD)	74.2(14.8)	62.9 (16.8)	57.1 (9.8)	$p = 0.022$
Time since amputation (years), mean (SD)	5.8(8.5)	9.7 (13.9)	20.7 (21.2)	$p = 0.104$
Indication, n (%)				$p = 0.125$
PVD	4 (8.7%)	7 (15.2%)	7 (15.2%)	
Trauma	1 (2.2%)	4 (8.7%)	14 (30.4%)	
Other	0 (0%)	2 (4.3%)	7 (15.2%)	
Employed, n (%)	0 (0%)	3 (23%)	13 (46%)	$p = 0.077$

PVD, peripheral vascular disease; other indications for amputation include congenital, infection and tumor.

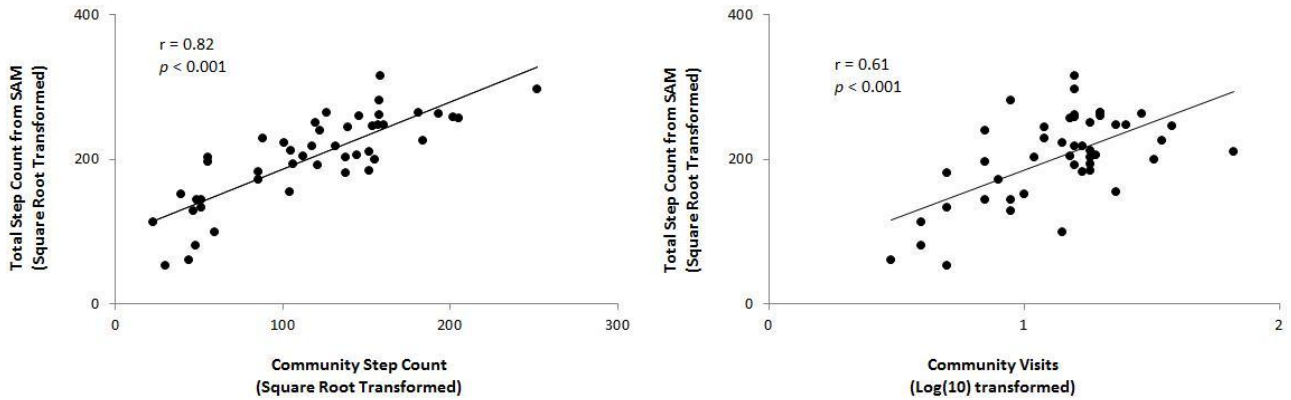
There were differences between *K*-level groups for gait velocity ($F_{(2,43)} = 28.5$, $p < 0.001$) and 6MWT distance ($F_{(2,43)} = 22.8$, $p < 0.001$). Post-hoc analysis revealed K1/2 amputees had significantly lower gait velocity than K3 amputees (95%CI 0.11–0.60, $p = 0.002$) and K4 amputees (95%CI 0.40–0.85, $p < 0.001$). Amputees categorised as K3 had significantly lower gait velocity than K4 amputees (95%CI 0.11–0.42, $p < 0.001$). For the 6MWT, post-hoc analysis revealed K1/2 amputees walked significantly less distance than K4 amputees (95%CI 119.6–309.1, $p < 0.001$). Amputees categorised as K3 walked significantly less distance than K4 amputees (95%CI 62.2–193.2, $p < 0.001$). There was no difference between K1/2 and K3 amputees ($p = 0.125$). A summary of community and clinic based measures for each *K*-level group is provided in Table 3.

Table 3. Mean (SD) community and clinical measures for *K*-level categories.

	K1/2 (*n* = 5)	K3 (*n* = 13)	K4 (*n* = 28)
Community Step Count	1,379(1,012)	14,483 (16,585)	19,463 (11,016)
Community Visit	7.2(4.3)	13.77 (5.8)	19.32(12.4)
Gait Velocity (m/s)	0.65 (0.2)	1.01 (0.2)	1.28(0.2)
6MWT (m)	212.0 (79.4)	298.6 (74.5)	426.3(79.8)

6MWT, six minute walk test.

Figure 2. Pearson correlation analysis of total step count (obtained from the SAM) over a seven day period and our measure of community activity (**left**) and community participation (**right**). In both instances there was a significant positive correlation indicating that activity data from a single accelerometer device (e.g., SAM) may provide good indication of community activity and participation.



There was a significant positive correlation between our defined measure of community activity (community based step counts) and total step counts obtained from the SAM alone ($r = 0.82$, $p < 0.001$). There was also a significant positive correlation between our defined measure of community participation (number of community visits) and total step counts obtained from the SAM alone ($r = 0.61$, $p < 0.001$) (see Figure 2).

4. Discussion

This study investigated community activity and participation of transtibial amputees using a simple approach to linking data recorded from separate commercially available accelerometer and GPS devices. Findings from this study demonstrate that data collected from a combination of accelerometer and GPS devices is feasible with a patient group over a seven day period, and the data obtained from these devices had limited interruption due to inadequate GPS signal.

Amputee participants were below the recommended daily step counts for healthy adults, and fall into the category of ―low activity‖ [36]. Additionally this study showed that K3 and K4 transtibial amputees demonstrated a wide range of actual community activity and participation levels, which likely contributed to non-significant statistical difference between these functional categories for the measures of community activity and participation. These findings are in contrast to clinically assessed measures of gait velocity and endurance (6MWT) which were able to differentiate the K3 and K4 functional categories. This suggests that while K4 transtibial amputees have the functional capacity to perform at a higher level in the community, in practice many do not achieve levels of community activity and participation greater than that of K3 amputees.

Community activity and participation are key indicators of successful rehabilitation and intervention effectiveness [1,5]. Recent advances in wearable technology have provided rehabilitation clinicians easier access to means of quantifying measures of activity and participation for a range of applications [21,22,37–42]. For amputee rehabilitation, wearable technology may be clinically appropriate to aid prosthetic prescription and to guide rehabilitation interventions. Similar data has been used previously in a case study [29] and we believe this to be the first study to report linked accelerometer and GPS data in a cohort of transtibial amputees. The methodology presented here may be transferable to other patient populations. The accuracy of wearable GPS devices integrated with geographic information allowed recording of a range of categorised community participation events. Linked SAM and GPS data provided an opportunity to analyse step counts in these categorised locations, and in the community in general, as a measure of community activity. Here we were able to demonstrate amputees performed the majority of activity within the home. For community based activity, the majority was performed in the work place for those amputees who were employed, and the most common community participation was visiting commercial facilities (shopping centres and local shops). The selection of participation events was based on typical activities of amputees, but could be modified and adapted for various patient populations as required. Although GPS devices have potential use in rehabilitation and research of clinical populations there are technical limitations. Primarily, GPS devices rely on satellite signal and have limited capacity for indoor use [28]. Data from this study demonstrates that a small proportion (6.5%) of data recording was lost from the GPS data due to insufficient satellite signal which occurred as a result of monitoring everyday activities in this cohort

of amputees. This small proportion compares well to previous activity monitoring studies in stroke which report acceptable GPS data loss of 13% [43].

To our knowledge this to be the first study to report community activity and participation from linked accelerometer and GPS data in a transtibial amputee population. This study defined community activity and participation as community based step counts and community visits based of previous literature [5,35]. From linked SAM and GPS data we were able to demonstrate that amputees categorised as K1 or K2 performed at lower community activity and participation levels than amputees categorised as either K3 or K4. This finding is not unexpected given that these higher functioning amputees had higher rates of employment. Interestingly there was no statistical difference in community activity and participation between amputees categorised as K3 and K4, most likely due to the wide range of community activity and participation levels within these two groups. This may be surprising given the discrepancies in employment status between these two groups. Objective clinical measures also confirm that K4 amputees do indeed have the functional capacity to perform at higher levels than K3 amputees [15,16]. A potential reason for this lack of significant difference in community activity and participation between K3 and K4 amputees relates to properties of this assessment. There are no subcategories within each *K* level. Therefore the difference between a high level K3 and low level K4 are likely to be minimal. Conversely, the differences between a low K3 and a high K4 may be quite large in comparison. Additionally, this system was developed to predict prosthetic requirements of amputees based on their likely requirements in the community. These categories provide indication of the most suitable prosthetic componentry, and do not reflect actual performance. Therefore, these findings may indicate that the predictive K level categories may not reflect actual community activity and participation levels.

Previous literature suggests age [44–48], comorbidities [44,46] and indication for amputation [46] to be factors potentially limiting amputees to perform functionally in the community. Differences in age were found between the K1/2 and K4 amputees. We would expect to find these differences as previous studies indicate that lower functioning amputees are typically older [49]. Therefore the functional differences between K1/2 and K4 amputees may be a combination of lower functional abilities and older age. However, we were unable to demonstrate difference between K3 and K4 amputees for both age and indication for amputation suggesting these factors have not limited performance of K4 amputees in the community. Further research in a larger cohort of amputees should be undertaken to decipher implications of these findings and investigate why amputees categorised as K3 and K4 perform functionally similar in terms of community activity and participation. Clinical implications of this study suggest higher functioning amputees, categorised as K3 and K4, do not achieve the recommended daily step counts required for active lifestyles [36]. These higher functioning amputees may require objective community measures (such as accelerometers of GPS devices) to more accurately determine differences in functional abilities, rather than commonly adopted clinical measures (*i.e.*, gait velocity and endurance). While the combination of separate accelerometer and GPS devices may present difficulties in linking the data and interpretation clinically, we demonstrated positive correlations between accelerometer data (total step count) on its own obtained from the SAM and our measures of community activity and participation. Hence, a simple accelerometer device to assess step-count activity may be an appropriate assessment to differentiate amputees' categorised as K3 and K4 and should be considered for clinical use.

Study Limitations

There are several limitations to this study which should be acknowledged. First, due to lost GPS signal, 5.3% of step count data was lost in the data linkage procedure. Although this percentage is low, it may represent a potential bias in this procedure and subsequent data analysis. Second, the data linkage procedure may limit the clinical usefulness of this methodology. However, we have shown a high correlation with total step count and our measure of community activity, and a moderate correlation with total step count and our measure of community participation. Third, we acknowledge the measure of community participation adopted may not completely encompass all aspects of community participation as described by the ICF [5]. For example, employment, social and recreational roles may be fulfilled from within a person's home, and therefore the exclusion of this data may not accurately represent community participation. However, a recent review summarised community participation as involvement in activities that occur outside the home, or involve a non-domestic nature [50]. We also suggest that participation in activities outside the home present greater mobility and social challenges, and are likely to represent greater community integration. Fourth, this study may also have benefited from inclusion of a participant diary to record daily community activity and participation. Although participation events were confirmed verbally with participants where required, it has previously been reported that a diary should be included in these studies to aid confirmation of activities, despite accuracy of diary recorded information being inferior to GPS recorded data [13,43]. Inclusion of a travel diary may have aided information recall in these instances. Fifth, results of this study with unilateral transtibial amputees may not be generalisable to other amputee populations, and further investigation is required to determine activity and participation of individuals with different levels of amputation; Finally, amputees recruited to participate in this study were primarily higher functioning (K3 and K4), with a relatively high percentage of traumatic amputees, and lower percentage of vascular amputees compared to that normally found in prosthetic rehabilitation services [51]. We suggest this is likely due to the long post-operative period in this study, and the poor mortality rates following rehabilitation for vascular amputees [52]. These results may not accurately reflect lower functioning K1 amputees, or more recent amputees. Despite this, we still observed relatively low activity levels amongst recruited amputees.

5. Conclusions

This study demonstrated a simple methodology to link step count and GPS data to assess community activity and participation in a group of unilateral transtibial amputees. We found amputees predicted to be higher functioning performed better in clinical assessments of gait velocity and endurance. However, they exhibited a wide range of community activity and participation levels. Therefore differences in *K*-levels may not accurately predict actual community activity or participation in higher functioning transtibial amputees. Step count data obtained from the SAM was shown to have a high correlation with community activity and participation and may be a good clinical tool to stratify higher functioning amputees based on actual activity as opposed to predicted activity.

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Author Contributions

Brenton Hordacre contributed to the overall study design, data collection, and writing of the manuscript. Christopher Barr contributed to the overall study design and writing of the manuscript. Maria Crotty contributed to the overall study design and writing of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Appendix 4

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DISORDERS OF THE NERVOUS SYSTEM

Ipsilateral corticomotor excitability is associated with increased gait variability in unilateral transtibial amputees

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Keywords: amputation, human, ipsilateral, motor cortex, transcranial magnetic stimulation

Abstract

Ipsilateral primary motor cortex (M1) reorganisation after unilateral lower-limb amputation may degrade function of the amputated limb. We hypothesised unilateral lower-limb amputees would have a bilateral increase in corticomotor excitability, and increased excitability of ipsilateral M1 would be associated with increased step-time variability during gait. Twenty transtibial amputees (16 male) aged 60.1 years (range 45–80 years), and 20 age- and gender-matched healthy adult controls were recruited. Single-pulse transcranial magnetic stimulation assessed corticomotor excitability. Two indices of corticomotor excitability were calculated. An index of corticospinal excitability (ICE) determined relative excitability of ipsilateral and contralateral corticomotor projections to alpha-motoneurons innervating the quadriceps muscle (QM) of the amputated limb. A laterality index (LI) assessed relative excitability of contralateral projections from each hemisphere. Spatial-temporal gait analysis was performed to calculate step-time variability. Amputees had lower ICE values, indicating relatively greater excitability of ipsilateral corticomotor projections than controls ($P = 0.04$). A lower ICE value was associated with increased step-time variability for amputated ($P = 0.04$) and non-amputated limbs ($P = 0.02$). This association suggests corticomotor projections from ipsilateral M1 to alpha-motoneurons innervating the amputated limb QM may interfere with gait. Cortical excitability in amputees was not increased bilaterally, contrary to our hypothesis. There was no difference in excitability of contralateral M1 between amputees and controls ($P = 0.10$), and no difference in LI ($P = 0.71$). It appears both hemispheres control one QM, with predominance of contralateral corticomotor excitability in healthy adults. Following lower-limb amputation, putative ipsilateral corticomotor excitability is relatively increased in some amputees and may negatively impact on function.

Introduction

Bipedal locomotion is the quintessential form of ambulation mastered by humans early in life. Activation of the primary motor cortex (M1) of both cortical hemispheres is essential for lower-limb motor control (Luft *et al.*, 2002; Sahyoun *et al.*, 2004), and amputation presents a unique challenge to the bi-hemispheric control of gait. Interestingly, it appears there is bilateral reorganisation of M1 following amputation (Schwenkreis *et al.*, 2003; Hordacre & Bradnam, 2013). Reorganisation of M1 contralateral to the side of amputation ($M1_{CON}$) increases cortical excitability and is well characterised (Hall *et al.*, 1990; Cohen *et al.*, 1991; Fuhr *et al.*, 1992; Kew *et al.*, 1994; Chen *et al.*, 1998). A concomitant increase in corticomotor excitability ipsilateral to the side of amputation ($M1_{IPSI}$) has not been thoroughly investigated. There is evidence that $M1_{IPSI}$ undergoes reorganisation, likely due to high sensorimotor demand placed on the non-amputated limb early in rehabilitation (Hordacre & Bradnam, 2013). How a bilateral increase in M1 excitability might affect gait in lower-limb amputees is an important question for amputee rehabilitation given the challenges with prosthetic gait and risk of falls (Miller *et al.*, 2001; Pauley *et al.*, 2006). The relationship between M1 excitability and function has not been addressed in studies to date. The spatial-temporal parameter, step-time variability, is a measure indicative of falls risk in older adults (Verghese *et al.*, 2009; Brach *et al.*, 2010) and transtibial amputees (Parker *et al.*, 2013). There is little understanding regarding cortical contributions to gait variability in the healthy population, or how amputation affects cortical excitability and gait variability in amputees.

Bilateral cortical reorganisation is not unique to amputees. Interhemispheric imbalance from suppression of the ipsilesional and facilitation of the contralesional hemisphere controlling the paretic upper-limb in chronic stroke is associated with poor recovery (Shimizu *et al.*, 2002; Murase *et al.*, 2004; Grefkes *et al.*, 2008). Assessing brain neurophysiology with transcranial magnetic stimulation (TMS) can identify hemispheric imbalance and quantify its impact on function. A laterality index (LI) of contralesional to ipsilesional excitability recorded from the non-paretic and paretic limbs, respectively, is one method (Brouwer & Schryburt-Brown, 2006; Wang *et al.*,

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2012). A ratio of contralesional to ipsilesional corticomotor projections to the paretic lower-limb, the index of corticospinal excitability (ICE), is another. In the latter, upregulation of ipsilateral corticomotor projections from the contralesional hemisphere is associated with poor lower-limb control in stroke (Madhavan *et al.*, 2010; Jayaram *et al.*, 2012). Our rationale for this current study was that a similar upregulation of ipsilateral projections to the amputated limb would degrade gait in lower-limb amputees. The primary aim was to investigate bilateral corticomotor excitability in healthy adults and lower-limb amputees using two neurophysiological indices, the LI and ICE. The secondary aim was to assess if there was an association between neurophysiological indices and gait function. We hypothesised lower-limb amputees would have a bilateral increase in corticomotor excitability, and greater excitability of putative ipsilateral corticomotor projections would be associated with increased step-time variability, indicating reduced function.

Materials and methods

Participants

Twenty unilateral transtibial amputees (16 male), with a mean age of 60.1 years (range 45–80 years), and 21.7 years (SD 22.3) since amputation were recruited. The amputee mobility predictor was used to determine function and categorise K-levels (Gailey *et al.*, 2002). Higher K-level scores indicate greater function (range K1–K4). The description of K-levels is as follows: K1 non-community ambulatory; K2 limited community ambulatory; K3 unlimited community ambulatory; and K4 high-functioning ambulator (Gailey *et al.*, 2002). Amputees of K1 level were excluded from the study as they were unable to perform functional gait assessment. A comparator group of 20 age- and gender-matched healthy adults was purposively recruited as control participants [mean age 59.3 years (range 43–83 years)]. Limb dominance was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), and in control participants the non-dominant limb was modelled as the amputated limb. Amputee and control participant demographics and clinical characteristics are summarised in Table 1. Potential participants with contraindications for TMS, including those with metallic implants, a history of seizures and medications known to alter CNS excitability, were excluded (Rossi *et al.*, 2009) following screening by a rehabilitation physician. Ethical approval was provided by the Southern Adelaide Clinical Human Research Ethics Committee, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Protocol

Participants attended a single session to assess brain neurophysiology and spatial-temporal gait parameters. During TMS, participants were seated comfortably with hip and knee joints flexed to 90°. A seated knee-extension task was used to unilaterally pre-activate the quadriceps muscle (QM) prior to each TMS pulse in response to an auditory cue repeated at 0.2-Hz intervals. Consistent muscle activation at 10–15% MVC was achieved by monitoring visual feedback of raw electromyography (EMG) signal from the QM. Transcranial magnetic stimulation pulses were triggered during muscle contractions using Signal software (v5.09).

Electromyography

Surface EMG was recorded from the QM bilaterally using 10-mm-diameter Ag/AgCl electrodes (Ambu, Ballerup, Denmark) placed 2 cm apart over the muscle bellies, with the distal electrode approximately 12 cm superior to the midpoint of the patella. A 20-mm-diameter ground Ag/AgCl electrode (3M Health Care, St Paul, MN, USA) was placed over the patella. Prior to affixing the electrodes, hair was removed by shaving, and the top layer of skin lightly abraded for optimal contact. EMG signals were sampled at 2000 Hz (CED 1401;

TABLE 1. Participant demographics and clinical characteristics

Amputee participants									Control participants				
Age	Sex	Dom limb	Indication	Time amp	Amp side	ICE	LI	K level	Age	Sex	Dom limb	ICE	LI
50	M	Right	Trauma	15.5	Left	0.40	0.01	4	50	M	Right	0.75	0.56
61	M	Right	Trauma	42.7	Right	0.92	0.54	4	60	M	Right	0.91	0.24
49	M	Right	Trauma	31.3	Right	0.08	0.42	4	51	M	Right	0.50	−0.10
64	M	Left	Trauma	3.7	Left	−0.50	0.29	4	66	M	Right	0.69	0.18
57	M	Right	Infection	53.9	Right	0.80	−0.33	4	57	M	Right	0.86	−0.18
80	M	Right	Tumour	57.7	Left	0.22	−0.92	4	83	M	Right	0.28	−0.23
65	M	Right	Other	7.2	Left	0.37	−0.55	4	66	M	Right	0.38	−0.09
60	M	Right	Trauma	20.9	Right	−0.13	−0.53	2	59	M	Left	0.26	0.60
61	M	Right	Other	1.5	Right	−0.14	−0.47	4	60	M	Right	0.63	−0.59
55	M	Right	PVD	5.0	Left	0.58	−0.74	4	53	M	Right	0.05	−0.34
61	M	Right	Trauma	59.7	Left	0.60	−0.11	4	59	M	Right	0.94	0.46
51	M	Right	PVD	0.7	Right	0.11	0.17	4	52	M	Right	0.33	−0.07
67	M	Right	PVD	6.4	Left	0.54	−0.35	3	67	M	Left	0.09	−0.82
45	M	Right	Trauma	9.2	Right	0.58	−0.14	4	43	M	Right	0.01	−0.71
61	M	Right	Trauma	41.6	Right	0.18	0.48	4	64	M	Right	0.66	0.68
55	M	Right	PVD	0.8	Left	0.63	0.39	3	54	M	Right	0.55	−0.06
53	F	Right	Trauma	17.0	Right	−0.15	−0.55	3	53	F	Right	0.26	−0.28
60	F	Right	Congenital	57.8	Right	0.11	−0.34	4	59	F	Right	0.45	−0.14
68	F	Right	PVD	1.1	Right	−0.09	0.61	3	60	F	Right	0.46	0.27
78	F	Right	PVD	0.9	Right	0.06	0.41	2	70	F	Right	0.40	−0.02

Age and time since amputation are reported in years. Indication of 'Other' includes undetected medical condition, and blood clot in limb. K Levels indicate amputee functional ability. K2 is a limited community ambulator who has ability to traverse low level environmental barriers such as curbs, stairs or uneven surfaces; K3 is a community ambulator capable of traversing most environmental barriers and is capable of ambulation with variable cadence; K4 is a ambulator capable of high impact, stress or energy levels and is typical of an active adult or athlete. Amp Side, side of amputation; Dom Limb, dominant limb; F, female; ICE, index of corticospinal excitability; LI, laterality index; M, male; PVD, peripheral vascular disease; Time Amp, time since amputation.

Cambridge Electronic Design, Cambridge, UK), amplified (CED 1902; Cambridge Electronic Design), band-pass filtered (20–1000 Hz) and stored for offline analysis (Signal v5.09).

Transcranial magnetic stimulation

Single-pulse TMS was delivered using a Magstim 200 stimulator (Magstim Company, Dyfed, UK). A flat 70-mm wing diameter, figure-eight coil was held tangentially over the scalp with the handle pointing 30° posterior-medially in the transverse plane. This coil orientation was determined from extensive piloting (Hordacre & Bradnam, 2013). As a guide, the coil was initially positioned 1 cm posterior, 1.5 cm lateral to the vertex (Madhavan *et al.*, 2010; Hordacre & Bradnam, 2013). The 'hotspot' for evoking maximal responses in the contralateral active QM was then determined for each M1 by systematically moving the coil over a 1-cm grid from this location and marked on the scalp. Active motor threshold (AMT) was determined separately for each M1 as the minimum stimulus intensity eliciting a 100-μV motor-evoked potential (MEP) in five of 10 stimuli in the contralateral QM (Rossini *et al.*, 1994). The stimulus intensity evoking a maximal MEP response (MEP_{MAX}) in the contralateral QM was determined for each M1. Three stimulus–response (S–R) curves were constructed from MEPs recorded at equally spaced intensities between AMT and MEP_{MAX} (inclusive). Two S–R curves were constructed from MEPs at six different intensities in each QM following stimulation of the respective contralateral M1 (contralateral S–R curves). A third S–R curve was constructed from MEPs recorded in QM of the amputated limb following stimulation of $M1_{IPSI}$ (ipsilateral S–R curve). The ipsilateral S–R curve was constructed with one additional stimulus intensity above MEP_{MAX} to account for higher thresholds to evoke ipsilateral MEPs (Ziemann *et al.*, 1999), which usually equated to 90–95% maximum stimulator output (MSO). For each intensity of the S–R curve, 14 MEPs were collected in random order.

Responses where pre-stimulus root mean square EMG (rmsEMG) were 2 SD above or below the mean were removed prior to averaging (range 0–2) to ensure consistency of MEP responses. From the retained traces, MEPs were measured peak-to-peak, averaged and plotted against stimulus intensity. The slope of the S–R curve was determined from the linear portion by linear regression. A computerised mathematical algorithm was used to determine the steepest section of the S–R curve. The algorithm used a sliding window of different combinations of consecutive points along the S–R curve (minimum 3, maximum all) to systematically select those that made up the steepest slope (SR_{SLOPE}; Fig. 1). SR_{SLOPE} was used to calculate two indices of corticomotor excitability for each participant. First, ICE assessed excitability of contralateral and ipsilateral corticomotor projections to the amputated limb (Madhavan *et al.*, 2010). Negative ICE values indicated relatively greater excitability of ipsilateral, compared with contralateral, descending corticomotor projections. The equation to calculate ICE:

$$\mathrm{ICE} = \frac{(\text{contralateral } SR_{SLOPE} - \text{ipsilateral } SR_{SLOPE})}{(\text{contralateral } SR_{SLOPE} + \text{ipsilateral } SR_{SLOPE})}$$

Second, a LI was determined to assess excitability of contralateral corticomotor projections innervating the amputated and non-amputated limb, respectively. Negative LI values indicate relative greater excitability of contralateral projections to alpha-motoneurons innervating QM of the non-amputated limb. Positive LI values indicate relative greater excitability of contralateral projections to alpha-motoneurons innervating QM of the amputated limb. The equation to calculate LI:

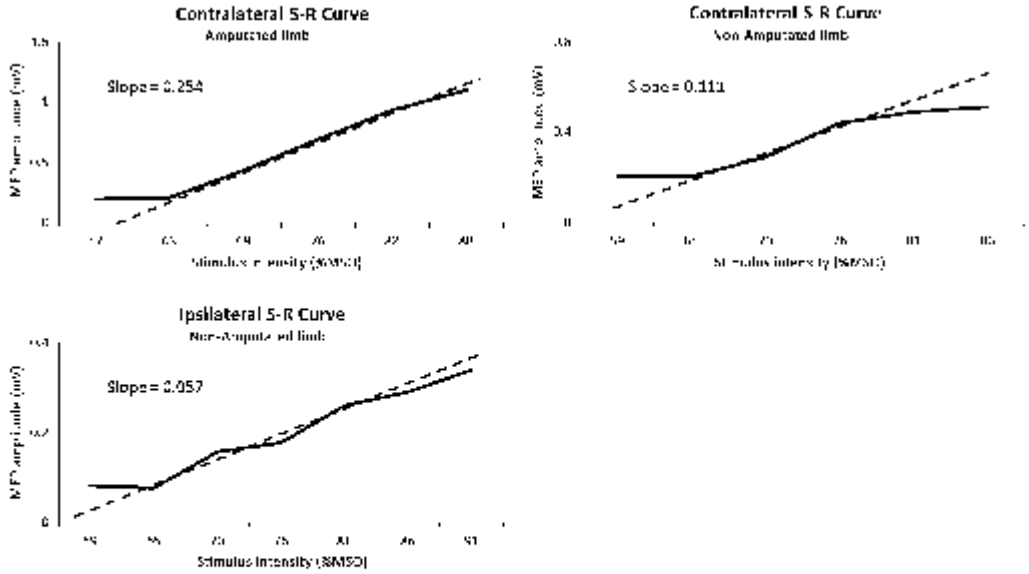

FIG. 1. A representative example of the three S–R curves from an amputee participant. SR_{SLOPE} was calculated from the steepest section of the curve (minimum three points, maximum all) using linear regression (represented by the dotted line). Index of corticospinal excitability and LI for this participant were 0.63 and 0.39 respectively. Motor-evoked potential, motor evoked potential; MSO, maximum stimulator output; mV, millivolts.

$$LI = \frac{(\text{contralateral } SR_{SLOPE}\, MI_{CON} - \text{contralateral } SR_{SLOPE}\, MI_{IPSI})}{(\text{contralateral } SR_{SLOPE}\, MI_{CON} + \text{contralateral } SR_{SLOPE}\, MI_{IPSI})}$$

The ipsilateral silent period (ISP) was used to assess interhemispheric inhibition from stimulation of MI_{IPSI} at 80% MSO (Chen *et al.*, 2003; Trompetto *et al.*, 2004; Avanzino *et al.*, 2007). This intensity was chosen because at higher intensities the onset of the ISP was often masked by the MEP. Data were rectified and averaged, and the ISP measured from this average. Ipsilateral SP onset was defined when post-stimulus EMG fell below the mean of the pre-stimulus EMG for a continuous period of 10 ms in a window 20–80 ms after the stimulus. Ipsilateral SP offset was defined when EMG returned to baseline levels (Chen *et al.*, 2003; Trompetto *et al.*, 2004; Avanzino *et al.*, 2007). The ISP was calculated as the area between onset and offset points relative to the mean of the prestimulus rmsEMG (ISP_{AREA}), expressed in mV/ms (Fig. 2).

Spatial-temporal gait variability

Spatial-temporal gait was assessed using an instrumented GAITRite walkway (CIR-Systems Inc., Sparta, NJ, USA) with embedded pressure sensors to capture individual footfall data over an active area 4.9 × 0.6 m. Participants completed 10 consecutive passes over the GAITRite at their self-selected comfortable walking speed. Data were sampled at 120 Hz and analysed using GAITRite software (version 4.5.5). Variability of spatial-temporal parameters was assessed by the coefficient of variation (CoV), calculated as SD divided by the mean expressed as a percentage. The primary gait outcome measure, step-time variability, is a velocity-dependent parameter, and greater variability can occur in raw data with variations in walking speed between trials (Beauchet *et al.*, 2009). Individual gait trial parameters were therefore normalised to a walking speed of 1 m/s for all participants prior to calculation of CoV in accordance with similar previous studies (Hof, 1996).

Data analysis

The normality of data was checked with a Shapiro–Wilk test. *Post hoc* tests explored significant effects and were corrected for multiple comparisons using a modified Bonferroni correction (Rom, 1990). The significance level was set at $P \leq 0.05$, and SPSS software was used for all statistical analyses (IBM Corp., Released 2010, IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY, USA).

Corticomotor excitability

Differences between amputee and control ICE, LI and ISP_{AREA} were tested with separate independent *t*-tests. To further understand fundamental contributions of each hemisphere to ICE ratios, SR_{SLOPE} and MEP latencies were separately analysed using one-way ANOVAs. The four independent variables were: amputee contralateral; amputee ipsilateral; control contralateral; control ipsilateral. To understand how the contralateral and ipsilateral SR_{SLOPE} contributed to ICE in amputees, correlation analysis was performed between ICE and ipsilateral SR_{SLOPE}, ICE and contralateral SR_{SLOPE}, and between the ipsilateral and contralateral SR_{SLOPE} used in the ICE calculations. To further understand fundamental contributions of each hemisphere to LI ratios, SR_{SLOPE} and MEP latencies were separately analysed using one-way ANOVAs. The four independent variables were: amputee amputated; and non-amputated limb; control dominant; and non-dominant limb. Background EMG was compared across the two contralateral S–R curves with a two group (amputee, control) × 6 condition (S–R curve intensities) ANOVA. Similarly, a two group (amputee, control) × 7 condition (S–R curve intensity) ANOVA was used for the ipsilateral S–R curve.

Functional gait variability

Step-time variability normalised to a walking speed of 1 m/s was assessed with a one-way ANOVA. The four independent variables were: amputee amputated; and non-amputated limb; and control dominant; and non-dominant limb.

Corticomotor excitability and gait function

Linear regression models analysed the association between the primary corticomotor excitability measures (ICE, LI) and step-time variability [normalised with log(10) transformation], and were

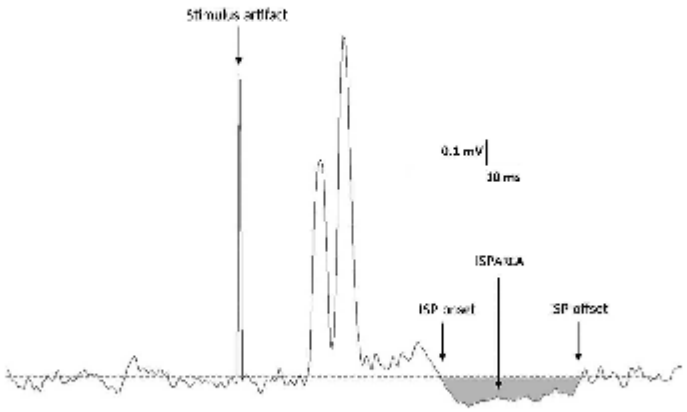

FIG. 2. A rectified ipsilateral MEP in a representative amputee participant demonstrating the ISP onset and offset (indicated by the arrows) used to calculate ISP_{AREA}. The trace is the average of 14 MEPs. The grey shaded area indicates ISP_{AREA}. ISP, ipsilateral silent period.

controlled for factors known to influence gait (age, time since amputation, stump length and indication for amputation; Gonzalez *et al.*, 1974; Gailey *et al.*, 1994; Kang & Dingwell, 2008; Callisaya *et al.*, 2010; Miaref *et al.*, 2010).

Results

No adverse events were experienced during TMS or gait analysis.

Corticomotor excitability measures

Corticomotor excitability measures are summarised in Table 2. Amputees had smaller ICE values than controls ($t_{38} = 2.07$, $P = 0.04$). Five amputees had negative ICE values, while no controls had negative ICE values. There were no significant differences between amputees and controls for LI ($P = 0.71$) or ISP_{AREA} ($P = 0.42$). The one-way ANOVA to elucidate fundamental contributions to the ICE ratio found a difference in SR_{SLOPE} ($F_{3,76} = 4.55$, $P = 0.006$). *Post hoc* analysis revealed amputees had steeper ipsilateral SR_{SLOPE} ($t_{38} = 1.96$, $P = 0.03$), but not contralateral SR_{SLOPE} ($P = 0.10$) compared with control subjects. As expected, contralateral SR_{SLOPE} was steeper than ipsilateral SR_{SLOPE} for both amputees ($t_{19} = 3.07$, $P = 0.006$) and controls ($t_{19} = 4.52$, $P = 0.001$). There were differences in MEP latency ($F_{3,76} = 6.05$, $P = 0.001$), with *post hoc* analysis revealing ipsilateral MEP onset latency was 1.5 ms longer than contralateral MEP onset latency for both amputees ($t_{19} = 3.03$, $P = 0.004$) and controls ($t_{19} = 2.98$, $P = 0.005$). Relative contributions of SR_{SLOPE} to smaller ICE ratios in amputees were analysed. There was no correlation between ICE and contralateral SR_{SLOPE} ($P = 0.17$), or ICE and ipsilateral SR_{SLOPE} ($P = 0.48$). There was a significant positive correlation between ipsilateral SR_{SLOPE} and contralateral SR_{SLOPE} ($r = 0.76$, $P = 0.001$; Fig. 3). The one-way ANOVA to elucidate fundamental contributions to the LI ratio showed a difference in SR_{SLOPE} ($F_{3,76} = 2.60$, $P = 0.05$). *Post hoc* analysis revealed contralateral SR_{SLOPE} evoked from stimulation of $M1_{IPSI}$ to be steeper in amputees than controls ($t_{38} = 1.70$, $P = 0.04$). SR_{SLOPE} evoked from stimulation of $M1_{CON}$ was no different between amputees and controls ($P = 0.10$). There was a difference in MEP latency ($F_{3,76} = 3.43$, $P = 0.02$), with *post hoc* analysis revealing amputee MEP latency measured on the amputated limb to be shorter than the non-amputated limb ($t_{38} = 2.46$, $P = 0.02$). There was no difference in MEP latency between sides for control subjects ($P = 0.98$). For amputees, the average background EMG for the amputated limb contralateral S–R curve was 0.04 mV (SD 0.03), for the non-amputated limb contralateral S–R curve was 0.06 mV (SD 0.05), and for the ipsilateral S–R curve was 0.04 mV (SD 0.02). For controls, the average background EMG for the non-dominant limb contralateral S–R curve was 0.05 mV (SD 0.02), for the dominant limb contralateral S–R curve was 0.04 mV (SD 0.02), and for the ipsilateral S–R curve was 0.04 mV (SD 0.02). There were no main effects of group (all $P > 0.12$) or intensity (all $P > 0.99$) for background EMG.

TABLE 2. Cortical excitability measures compared between amputee and control participants

Cortical excitability measure	Amputee Mean (SD)	Control Mean (SD)	Statistic
Con SR_{SLOPE} $M1_{CON}$	0.38 (0.39)	0.25 (0.20)	$P = 0.10$
Con SR_{SLOPE} $M1_{IPSI}$	0.61 (0.77)	0.30 (0.27)	$P = 0.04$*
Ipsi SR_{SLOPE} $M1_{IPSI}$	0.21 (0.27)	0.09 (0.09)	$P = 0.03$*
ICE	0.26 (0.37)	0.47 (0.28)	$P = 0.04$*
LI	−0.09 (0.47)	−0.03 (0.42)	$P = 0.71$
ISP_{AREA} (mV ms)	0.53 (0.38)	0.64 (0.50)	$P = 0.42$

Con, contralateral; ICE, index of corticospinal activity; Ipsi, ipsilateral; ISP, ipsilateral silent period; LI, laterality index; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex ipsilateral to the amputated limb; MEP, motor evoked potential.
*Significant at $P \leq 0.05$.

Functional gait variability

Normalised step-time variability for amputees was 5.15% (SD 2.7) on the non-amputated limb and 5.15% (SD 3.4) on the amputated limb. For control participants, normalised step-time variability was 4.77% (SD 1.4) on the dominant limb and 4.61% (SD 1.7) on the non-dominant limb. There were no significant differences in step-time variability ($P = 0.86$).

Corticomotor excitability and gait function

For amputees, linear regression models controlling for age, time since amputation, stump length and indication for amputation demonstrated a negative relationship between ICE and step-time variability on the amputated ($R^2 = 0.64$, $P = 0.04$) and non-amputated limb ($R^2 = 0.64$, $P = 0.02$; Fig. 4). No other independent variables controlled for were significant ($P > 0.12$). There was no relationship between LI and step-time variability for amputees on the amputated ($P = 0.55$) and non-amputated limb ($P = 0.79$). For control subjects there were no relationships between ICE and normalised step-time variability on the dominant ($P = 0.36$) or non-dominant limb ($P = 0.86$), or LI and normalised step-time variability on the dominant ($P = 0.95$) or non-dominant limb ($P = 0.75$).

Discussion

This study investigated bilateral corticomotor excitability and step-time variability in healthy adults and unilateral transtibial amputees. There were several findings with relevance for corticomotor control of the lower-limb and the effect of lower-limb amputation. In healthy adults there was bilateral cortical control of one QM, with a predominance of contralateral over ipsilateral excitability. In some amputees there was a change in the relative excitability between the hemispheres whereby greater ipsilateral, relative to contralateral, excitability lead to smaller ICE values. Smaller ICE values in amputees were associated with increased step-time variability on both the amputated and non-amputated limb. Contrary to our hypothesis, there was no bilateral increase in corticomotor excitability in amputees as contralateral M1 excitability was no different to controls. The LI was no different between amputees and controls. The results of this study and their putative implications for amputee rehabilitation are discussed below.

In the current study there was an increase in the ipsilateral SR_{SLOPE} recorded in the QM of the amputated limb, suggesting greater ipsilateral corticomotor excitability. This conclusion must be interpreted conservatively, however. A limitation of the TMS method used in this study is the 'hotspot' for lower-limb muscle representations is adjacent to the interhemispheric fissure, raising the question of whether the coil inadvertently stimulated both hemispheres. Certainly, ipsilateral responses to TMS in the lower-limb are a mix of ipsilateral and contralateral descending inputs as acknowledged previously (Madhavan *et al.*, 2010; Jayaram *et al.*, 2012). We cannot know what proportion of the responses used to calcuate SR_{SLOPE} in the current study were ipsilateral in origin.

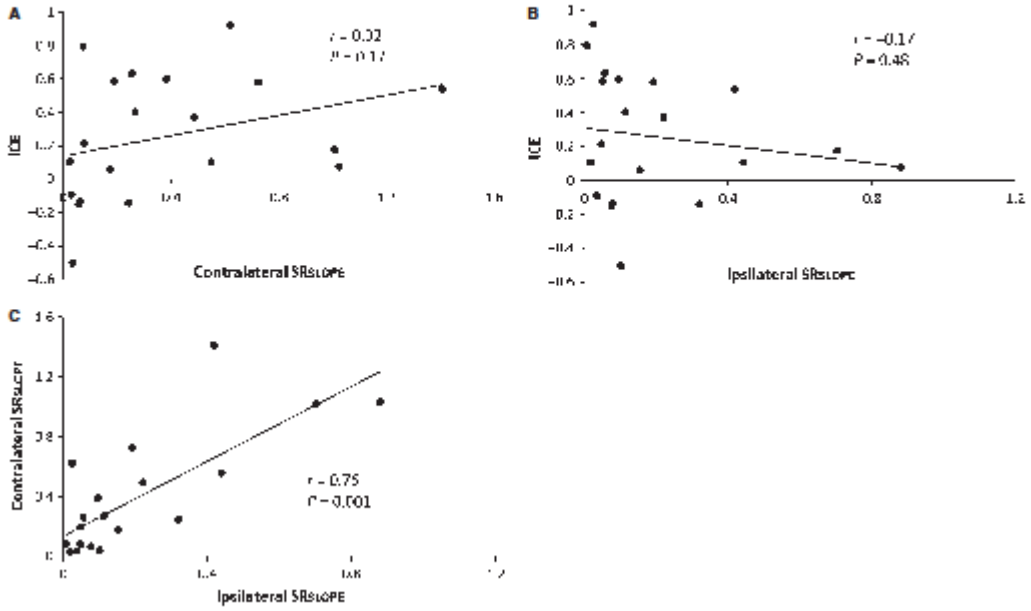

FIG. 3. Correlation analysis to determine relative contributions of contralateral and ipsilateral SR_{SLOPE} to ICE. Figure A and B illustrate that there was no correlation between contralateral SR_{SLOPE} and ICE, or ipsilateral SR_{SLOPE} and ICE. Figure C illustrates a positive correlation between contralateral SR_{SLOPE} and ipsilateral SR_{SLOPE}. ICE, index of corticospinal excitability; SR_{SLOPE}, slope values of the S–R curve.

However, our results indirectly suggest that a good proportion of the ipsilateral response was mediated from projections other than the contralateral corticospinal tract. Ipsilateral responses were greater in amputees, while contralateral responses recorded in the same QM were no different to controls. If the offset coil location for evoking ipsilateral responses was mostly stimulating the contralateral hemisphere, there should have been no difference between groups. Nonetheless, we cannot be sure, and refer to ipsilateral responses as 'putative' in the following discussion.

Motor control of the QM depends upon both ipsilateral and contralateral hemispheres in humans, although it appears predominance of the contralateral hemisphere is normal. Functional magnetic resonance imaging studies demonstrate that isolated knee flexion/extension and ankle dorsiflexion/plantar flexion movements activate both ipsilateral and contralateral M1 (Luft *et al.*, 2002; Sahyoun *et al.*, 2004). Our TMS findings progress this understanding by demonstrating a contralateral predominance of cortical excitability, as observed in healthy adults was not associated with gait variability. If following lower-limb amputation putative ipsilateral corticomotor excitability dominated over contralateral, there was an association with increased gait variability. While both hemispheres contribute to the control of human gait, it is evident that the balance of excitability between the M1s is critical for normal function. Unexpectedly there was no bilateral increase in corticomotor excitability in amputees as there was no difference in $M1_{CON}$ excitability between amputees and controls. This was surprising, as previous lower-limb amputee studies have reported reorganisation of $M1_{CON}$ in the forms of lower thresholds for TMS (Chen *et al.*, 1998), larger MEPs (Fuhr *et al.*, 1992), reorganisation of motor maps (Schwenkreis *et al.*, 2003), or a reduction in intracortical inhibition (Chen *et al.*, 1998). It is not obvious why $M1_{CON}$ excitability was unaffected in this group of amputees, but might relate to factors such as length of time since amputation and their relatively high ambulatory function. While contralateral corticomotor excitability over the non-amputated limb was greater in amputees, this did not influence the LI, which did not discriminate between amputees and control participants.

Amputees had smaller ICE values than controls, indicating relatively greater putative ipsilateral to contralateral corticomotor excitability. Smaller ICE values could potentially result from a steeper ipsilateral SR_{SLOPE}, or flatter contralateral SR_{SLOPE}. To elucidate which hemisphere contributed to negative ICE values, we separately correlated each M1 SR_{SLOPE} with ICE. There was no relationship for either hemisphere, indicating negative ICE was not an absolute increase in $M1_{IPSI}$ or decrease in $M1_{CON}$ excitability. Instead, it was those amputees with a 'relatively' greater putative ipsilateral to contralateral M1 excitability that demonstrated smaller ICE values. It is also likely that smaller ICE values indicate greater $M1_{IPSI}$ excitability than the suppression of $M1_{CON}$ because the ISP, assessing the degree of interhemispheric inhibition from $M1_{IPSI}$ to $M1_{CON}$, was similar for amputees and controls. Ipsilateral SPs evoked in the lower-limb are considered to be mediated by transcallosal pathways similar to the upper-limb (Lo & Fook-Chong, 2004). The ISP results, at least in part, from activation of interhemispheric projections across the corpus callosum from the stimulated hemisphere that inhibit the homologous area of the contralateral hemisphere (Chen *et al.*, 2003; Trompetto *et al.*, 2004). The net result of an increase in interhemispheric inhibition is suppression of corticomotor output from contralateral M1 (Ferbert *et al.*, 1992; Di Lazzaro *et al.*,

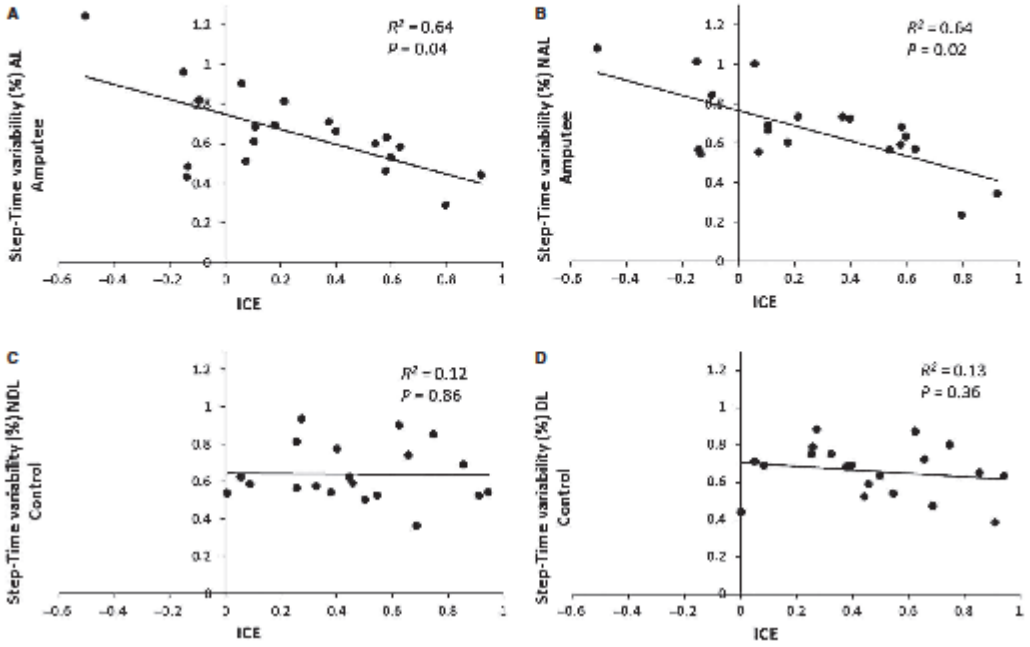

FIG. 4. Linear regression analysis of step-time variability normalised to a walking speed of 1 m/s (log (10) transformed) and ICE. Figure A and B illustrate step-time variability for the amputated and non-amputated limb in amputee participants. Figure C and D illustrate step-time variability of the non-dominant and dominant limb in control participants. Greater step-time variability was associated with smaller ICE values in amputees, but not controls. AL, amputated limb; DL, dominant limb; ICE, index of corticospinal excitability; NAL, non-amputated limb; NDL, non-dominant limb.

1999), evoking a longer ISP, which was not seen in the current study. Finally, increased interhemispheric inhibition would result in a negative LI value, which was also not observed. The findings of the present study indicate smaller ICE values in amputees compared with controls likely result from increased excitability of putative ipsilateral descending projections to the spinal cord.

Smaller ICE values in amputees were associated with increased step-time variability for both the amputated and non-amputated limb. Increased step-time variability is a predictor of higher falls risk in amputees (Verghese *et al.*, 2009; Brach *et al.*, 2010; Parker *et al.*, 2013). A causal relationship was not tested in the current study. However, the strong association between smaller ICE values and functional measures may indicate that upregulated putative ipsilateral projections degrade function, or alternatively compensatory gait patterns may increase excitability of putative ipsilateral corticomotor projections. Further studies are required to demonstrate cause and effect, and may prove ICE is a valid neurophysiological marker of reduced function in lower-limb amputees. It is unlikely that smaller ICE values in amputees were a direct result of the clinical characteristics or pathology leading to the amputation as those with negative ICE were a disparate group. This indicates changes in corticomotor excitability were independent of the clinical characteristics or pathology. The pathways responsible for the putative ipsilateral MEPs also cannot be determined from this study, but may involve reticulospinal projections descending to the spinal cord as suggested for the upper-limb following stroke (Ellis *et al.*, 2007, 2012; Schwerin *et al.*, 2008). Reticulospinal pathways bilaterally innervate axial and proximal alpha-motoneurons important for the control and postural support of muscles subserving locomotion (Drew *et al.*, 2004). Reticulospinal projections branch extensively as they terminate in the spinal grey matter (Peterson & Abzug, 1975; Matsuyama *et al.*, 1999), to link widely separated sections of the spinal cord (Lemon, 2008). Increased activity in the reticulospinal tract would lead to non-specific activation of muscles producing motor conflict that may degrade prosthetic gait (Kagerer *et al.*, 2003). Evidence of abnormal EMG patterns during amputee gait (Huang & Ferris, 2012) support the idea of motor conflict, and should be further investigated in gait variability studies.

There are two potential limitations of this study to consider. First, amputee participants were higher functioning and may not be representative of the community. Despite this, there were smaller ICE values in amputees with relatively poorer function. Second, there was a lack of homogeneity for indications for amputation across participants. In particular, vascular amputations have associated peripheral neuropathies and general deconditioning compared with trauma amputations. However, of the amputees with negative ICE, only one was a vascular amputee arguing against this confounding factor (Table 1). The indication for amputation was controlled for in our ICE and step-time variability regression analysis, and was a non-significant factor.

In conclusion, control of the QM during normal human gait may depend upon the relative corticomotor excitability between hemispheres; with a predominance of contralateral control. Following amputation, a change in the balance of cortical excitability might affect gait function. In the current study, amputees had smaller ICE

values compared with controls, and smaller ICE values were associated with increased step-time variability. This indicates an increase in putative ipsilateral to contralateral excitability may increase step-time variability, which may in turn lead to greater risk of falls in amputees. Future studies should seek to demonstrate causal relationships between measures of cortical neurophysiology, such as ICE, and gait function. This understanding would have the potential to improve amputee clinical practice.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgement

The authors acknowledge Orthotics and Prosthetics South Australia for assistance with participant recruitment.

Abbreviations

AMT, active motor threshold; CoV, coefficient of variation; EMG, electromyography; ICE, index of corticospinal excitability; ISP, ipsilateral silent period; LI, laterality index; M1, primary motor cortex; $M1_{CON}$, primary motor cortex contralateral to the amputated limb; $M1_{IPSI}$, primary motor cortex ipsilateral to the amputated limb; MEP, motor-evoked potential; MSO, maximum stimulator output; QM, quadriceps muscle; TMS, transcranial magnetic stimulation.

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Appendix 5

Reorganisation of primary motor cortex in a transtibial amputee during rehabilitation: A case report

Following amputation, reorganisation occurs predominately at the cortical level (Chen et al., 1998). Reorganisation of the primary motor cortex contralateral to the amputated limb (M1con) appears dependent upon a reduction in intracortical inhibition (Chen et al., 1998; Dettmers et al., 1999; Schwenkreis et al., 2000) resulting in reorganisation of proximal muscle representations (Cohen et al., 1991; Chen et al., 1998; Röricht et al., 1999). Reorganisation also occurs in primary motor cortex ipsilateral to the amputated limb (M1ipsi) (Schwenkreis et al., 2003) and may be secondary to reduced interhemispheric inhibition (Werhahn et al., 2002). These studies provide insight into chronic cortical reorganisation following amputation; however reorganisation in the sub-acute phase has not been reported. We present a longitudinal case study investigating bilateral M1 neurophysiology and function in a lower-limb amputee over the course of standard prosthetic rehabilitation (Hordacre et al. (in press)). We hypothesised that reorganisation would be observed in both M1con and M1ipsi, and would reflect adaptive plasticity in response to rehabilitation.

A 54 year-old, type-two diabetic male was recruited following a left transtibial amputation. Neurophysiological and functional measures were recorded in days post-surgery. The Amputee Mobility Predictor (AMP-PRO) (Gailey et al., 2002) assessed function; higher scores indicate greater functional ability. A healthy 52 year-old male was recruited for comparison. Neither participant used central nervous system altering medication during testing. Both participants were right handed, (amputee, 100; control, 93) (Oldfield, 1971). The control non-dominant limb was modelled as the amputated limb. The study had local ethics committee approval.

Surface EMG was recorded from rectus femoris (RF) bilaterally using 10 mm-diameter Ag/AgCl electrodes (Ambu, Ballerup, Denmark). A 20 mm-diameter ground Ag/AgCl electrode was fixed over the patella (3M Health Care, Canada). EMG signals were amplified (CED 1902; UK), band-pass filtered (20–1000 Hz), sampled at 2000 Hz (CED 1401; UK) and stored for offline analysis (Signal v5.07). Single-pulse TMS was delivered using a Magstim Model 200^2 stimulator, and paired-pulse TMS using two stimulators connected to a BiStim^2 unit (Magstim Company, Dyfed, UK). A flat 70 mm figure-eight coil was held tangentially over the scalp with the handle pointing 45° posterior-medially in the sagittal plane, and positioned 1 cm posterior, 1.5 cm lateral to the vertex to elicit maximal responses in the contralateral RF (Madhavan et al., 2010). Motor evoked potentials (MEPs) were evoked during phasic knee extension (10–15% maximal voluntary contraction) monitored by visual feedback of raw EMG. Active motor threshold (AMT) was determined separately for M1con and M1ipsi as the minimum intensity that elicited a 100 μV MEP in five of ten stimuli in the contralateral RF. For single-pulse TMS, 16 MEPs were evoked at 120%AMT. For paired-pulse TMS, 16 non-conditioned (NC) and 16 conditioned (C) MEPs were evoked in randomised order as short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). The test stimulus (TS) was set to produce a half maximum MEP (50%MEPmax). SICI was assessed using three conditioning-stimulus (CS) intensities (70%AMT, 80%AMT and 90%AMT) with an inter-stimulus-interval of 2 ms (Talelli et al., 2011), generating a SICI recruitment-curve (Peurala et al., 2008). LICI was assessed using a suprathreshold CS (50%MEPmax) delivered 100 ms before TS (McDonnell et al., 2006). MEPs were measured offline as peak-to-peak amplitudes and averaged (Signal v5.07). SICI and LICI were expressed as the difference between conditioned and non-conditioned MEP amplitude (%Inhibition = 100 − (C/NC × 100)). Linear regression analysis was performed between Time and AMT, MEPs, SICI and LICI, and between AMP-PRO and AMT, MEPs, SICI and LICI.

AMT of M1con was 60%MSO on admission and 64%MSO on discharge. AMT of M1ipsi was 67%MSO and 58%MSO at the same time-points (control 49%MSO M1con; 56%MSO M1ipsi). Linear regression revealed attenuation of M1ipsi AMT over time ($R^2 = 0.440$, $p = 0.037$). The average MEP in M1con was 0.24 mV on admission and 0.33 mV on discharge, and in M1ipsi was 0.90 and 0.21 mV, respectively (control 0.34 mV M1con; 0.65 mV M1ipsi). M1ipsi MEP amplitude was also attenuated over time ($R^2 = 0.533$, $p = 0.017$). Higher AMP-PRO scores were correlated with reduced AMT ($R^2 = 0.629$, $p = 0.006$) and reduced MEP amplitude ($R^2 = 0.500$, $p = 0.022$) for M1ipsi only.

In our amputee, the average test MEP to assess intracortical inhibition was 0.23 mV (SICI) and 0.26 mV (LICI) for M1con, 0.29 mV (SICI) and 0.28 mV (LICI) for M1ipsi. The control subject test MEP was 0.52 mV (SICI) and 0.59 mV (LICI) for M1con, and 0.70 mV (SICI) and 0.63 mV (LICI) for M1ipsi. Maximum SICI was observed at CS of 70%AMT in both M1con (21.8%) and M1ipsi (20.1%), compared to control (M1con, CS 80%AMT (19.6%); M1ipsi CS 90%AMT (22.5%)). No correlation was observed between SICI and time for either hemisphere. Interestingly SICI was variable across sessions (Fig. 1a), with no relationship between SICI and AMP-PRO (M1con $p = 0.745$; M1ipsi $p = 0.478$). LICI was 43.8% in M1con, and 35.1% in M1ipsi (admission), and 5.0% in M1con, and 7.3% M1ipsi (discharge) (control M1con 69.5%, M1ipsi 67.0%). LICI significantly decreased over time in M1con ($R^2 = 0.672$, $p = 0.004$), and also decreased in M1ipsi (trend) ($R^2 = 0.394$, $p = 0.052$) (Fig. 1b). Higher AMP-PRO scores were associated with reduced LICI in M1ipsi only ($R^2 = 0.551$, $p = 0.014$).

In this transtibial amputee SICI was variable while LICI reduced over time, indicating intracortical inhibition plays an important role in the sub-acute phase following amputation. A novel finding was that M1ipsi reorganised earlier than M1con, which appeared delayed until after the amputee was standing with the prosthetic limb.

AMT and MEP amplitude were comparable to the control at discharge. M1con MEP amplitude were small from admission to discharge compared to M1ipsi at admission. Previous studies demonstrate increased excitability in M1con muscle representations proximal to the site of amputation, reflected by larger MEP amplitudes (Cohen et al., 1991; Chen et al., 1998; Röricht et al., 1999). We are unsure why we observed consistently small MEP amplitude across time in M1con, but this may be due to MEP amplitudes being assessed with an active muscle rather than at rest as previously observed (Ridding and Rothwell, 1997). However, the observed reduction in M1ipsi AMT over time indicates intrinsic neuroplasticity in corticomotor neurons mediated by voltage-gated sodium channels (Ziemann et al., 1996), while reduction in M1ipsi MEP amplitude is attributed to modulation of synaptic transmission via glutamate receptors, and likely represents a LTD-like synaptic plasticity (Delvendahl et al., 2012). These mechanisms were not as evident in M1con.

We observed variable SICI over time and a steady reduction in LICI in both hemispheres. SICI and LICI represent distinct inhibitory systems, mediated by different post synaptic receptors (GABA-A and GABA-B) (Sanger et al., 2001). SICI has previously been reported to underpin amputation-induced plasticity in chronic amputees (Chen et al., 1998; Dettmers et al., 1999; Schwenkreis et al., 2000). Our study demonstrated SICI plays an important role in cortical reorganisation during the sub-acute phase. We found reduction in SICI in both M1con and M1ipsi, which appeared associated with rehabilitation phase (Fig. 1a). We suggest modulation of GABA-A receptor activity may be driven by functional tasks in rehabilitation as a result of use-dependent neuroplasticity.

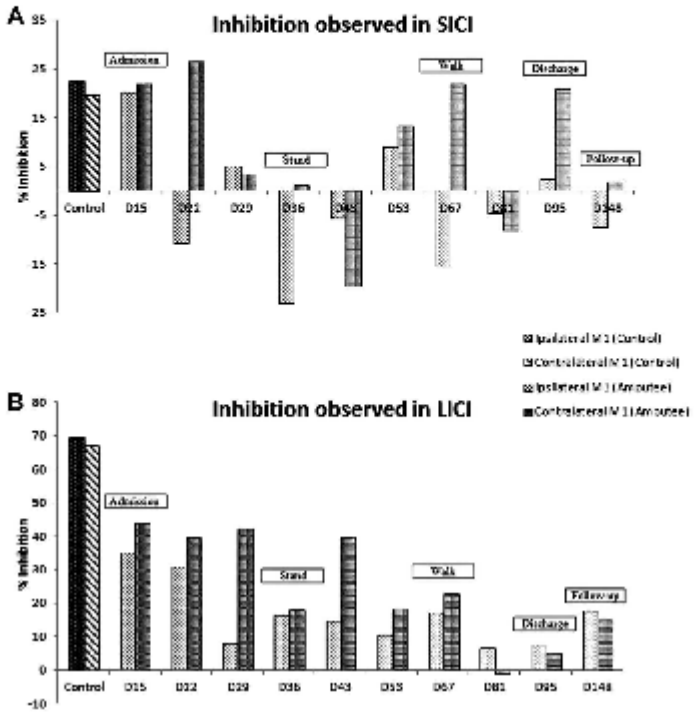

Fig. 1. Intracortical inhibition observed in the control subject and the amputee across rehabilitation (days since amputation) for (A) SICI and (B) LICI. Main rehabilitation phases are indicated. SICI was attenuated at key rehabilitation phases and recovered in between. LICI reduced steadily over rehabilitation.

However, our results may also reflect the high degree of variability often observed in SICI (Orth et al., 2003). Conversely, LICI gradually decreased over time, possibly indicating GABA-B receptor activation is less sensitive to activity dependent mechanisms (Fig. 1b). Both SICI and LICI were still reduced compared to our control at discharge.

This study reports M1con and M1ipsi reorganisation in a subacute amputee undertaking hospital-based rehabilitation. We believe this is the first report of its kind, with these results indicating an additional late phase of reorganisation associated with rehabilitation not previously reported in limb deafferentation (acute) or chronic amputee studies. We suggest that cortical reorganisation may be driven by use-dependent plasticity associated with rehabilitation phase in our high functioning amputee. Modulation of GABAergic inhibition appeared to be related to rehabilitation phase and was delayed in M1con. We hypothesise that early reorganisation of M1ipsi may influence that in M1con, perhaps due to interhemispheric interactions influencing SICI and LICI (Werhahn et al., 2002). Studies in stroke indicate balancing hemispheric excitability is important for functional recovery (Hallett, 2001). We propose early targeted amputated limb exercise may provide stimulation to drive optimum M1con reorganisation.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix 6

Consent to Participation in Research

Community Ambulation of Lower Limb Amputees

I, ...

(first or given names) (last name)

request and give consent to my involvement in the research project: Community Ambulation of Lower Limb Amputees

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....

(first or given names) (last name)

and my consent is given voluntarily.

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I acknowledge that the details of the following has been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

I understand that:

1. I will attend a single session at the Rehabilitation ward gymnasium located at the Repatriation General Hospital. The session will last approximately 1 hour.
2. The assessments are clinical tests and written questionnaires.
3. My medical records may be accessed to obtain results of outcome measures I have completed

4. I will be required to wear a step activity monitor for a 7 day duration which will be affixed to my prosthesis.
5. I will be required to carry a GPS device with me for a period of 7 days which will require the battery to be charged each night.
6. I will participate in the Amputee Community Ambulation study which will investigate mobility and balance measures of various levels of amputees living in the community to help characterise their functional abilities

I have understood and I am satisfied with the explanations that I have been given.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant: .....

Date: .....

I,..... have described to .....

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: .....

Date: .....

Status in Project:.....

Appendix 7

Participant Information Sheet

Community Ambulation of Lower Limb Amputees

Researchers

Brenton Hordacre

Dr Benjamin Patritti

Dr Chris Barr

Prof Maria Crotty

Invitation to participate

We would like to invite you to take part in this trial investigating community ambulation in lower limb amputees. The trial aims to collect information about the walking patterns of lower limb amputees when at home and in the community. Involvement in the trial is completely voluntary, and entirely your choice. Whether you take part or not, your decision will not affect your medical care with the health service at Repatriation General Hospital or Orthotics and Prosthetics South Australia (OPSA) in any way.

Selection

You are eligible for this trial because you are a lower limb amputee who has completed prosthetic rehabilitation and are now living in the community.

Aims of the project

The aims of this study are to develop a better understanding of walking and balance abilities of amputees who are living in the community. We will use the information we obtain to help categorise community abilities of amputee patients which may be used by clinicians to monitor the rehabilitation of patients.

Summary of procedures

If you agree to participate in this study, you will complete a short series of walking and balance assessments which will be conducted by the chief investigator (Brenton Hordacre) in the Rehabilitation ward gymnasium located at the Repatriation General Hospital. Rest sessions will be provided between assessments, with individual tasks lasting no longer than a few minutes each. You will also be asked to complete a small series of paper based questionnaires aimed at determining your ambulation ability since completing your prosthetic rehabilitation and living in the community. We will also provide you with a step activity monitor, which is a small device that will attach to your prosthesis, and count the number of steps you take daily for a period of seven days. This involves no significant requirement on your behalf, other than to wear your prosthesis (with step counter attached) for walking as you usually do. You will also be provided with a global positioning system (GPS) device which you will be required to carry with you for the same period of seven days when you wear the step activity monitor. The device may be worn on a belt loop, or alternatively carried in a pocket. The GPS device will collect data about distances and speeds travelled within the community. You will be required to charge the device each night. You will be provided with the required equipment and instructions on how to charge the device.

Access to your medical records may be required to obtain information relating to functional assessments you may have completed in the past.

Commitments

This study will involve a single session of approximately 1 hour duration. All assessments will be conducted at the Repatriation General Hospital.

Benefits

It is not anticipated you will directly benefit from participating in this study. Data collected may improve current clinical practice and this will benefit future patients who have experienced lower limb amputation.

Risks and adverse effects

Tasks involved in this study are no more strenuous than daily activities. The risks and adverse events associated with this study are considered very low. If you feel uncomfortable at any time during the experiment, please notify the researcher.

Compensation

If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is not automatic and you may have to take legal action to determine whether you should be paid.

Confidentiality

Under Australian privacy law all information collected about you must be kept confidential, unless you agree to it being released. If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities and by authorised people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentiality to you as a research participant and no information that could identify you will be given to anyone else. If the results of this study are published, for example in scientific journals, you will not be identified by name. To ensure that you will not be able to be identified, all participant information collected in this study will be de-identified.

Records and data about your participation in this study may be used for study purposes, to obtain regulatory approval for the study or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.

Publication

It is the intention of the researchers that project outcomes will be published in conference papers, journals or other venues as appropriate and will form part of a PhD thesis. You will not be identifiable in any publication or results of this study.

Withdrawal

Your participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in this study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive.

Outcomes

The results will be published in scientific journals. If you would like to be informed of the outcomes of the study you may leave your contact details with the researchers who will send you a letter in due course.

Expenses and payments

You will not receive any payment for participation in this study apart from compensation for any required reasonable travel costs for visits made during the study.

Contact

Should you require further details about the study at any time please contact Brenton Hordacre on (08) 8275 2835 or 0422056018.

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 6453 or email research.ethics@health.sa.gov.au

Appendix 8

Consent to Participation in Research

Neurophysiology of Community Dwelling Amputees

I, ...

(first or given names) (last name)

request and give consent to my involvement in the research project: Neurophysiology of community dwelling amputees

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....

(first or given names) (last name)

and my consent is given voluntarily.

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I acknowledge that the details of the following has been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

I understand that:

1. I will attend one session in the Applied Brain Research Laboratory, lasting approximately 2.5 hours at the Repatriation General Hospital.
2. The assessments are a questionnaire, clinical tests and Transcranial Magnetic Stimulation (TMS)
3. TMS involves the application of magnetic stimulation to the brain
4. My safety for TMS has been assessed using the participant safety questionnaire, signed by a hospital physician.

5. In the unlikely occurrence of an adverse event such as a seizure, medical support is available onsite at the Repatriation General Hospital.
6. I will participate in this study investigating community amputees and healthy control adults.

I have understood and I am satisfied with the explanations that I have been given.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant: .....

Date: .....

I,..... have described to .....

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: .....

Date: .....

Status in Project: .....

Appendix 9

Participant Information Sheet

Neurophysiology of Community Dwelling Amputees

Researchers

Brenton Hordacre

Dr Lynley Bradnam

Prof Maria Crotty

Invitation to participate

We would like to invite you to participate in this trial investigating how changes in the human brain following amputation may influence an amputee's ability to function in the community effectively. Involvement in the trial is completely voluntary, and entirely your choice. Whether you take part or not, your decision will not affect your medical care if you are currently receiving any with the health service at Repatriation General Hospital in any way.

Selection

You are eligible for this trial because you are either a lower limb amputee who has completed rehabilitation and is living in the community, or alternatively, you are considered a healthy subject who is age and gender matched to a lower limb amputee participant. Your eligibility will be further determined following completion of the TMS safety questionnaire. For example, you may not be eligible if you have a history of seizures, or have metal implants or fragments above the level of the shoulders. This is because there is a rare chance that TMS can induce seizures or cause metallic objects to move in the body.

Aims of the project

The study aims to assess brain reorganisation following amputation of community living amputees in comparison to healthy adults. It will also investigate if the brain reorganisation following amputation is related to the amputee's ability to integrate functionally back into the community.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and safe method to assess activity in the motor pathways and is used extensively around the world to study movement disorders. TMS involves a brief magnetic pulse applied over the area of your brain controlling the muscles of your arm, through a coil placed lightly on the scalp. Recordings are made from the muscles of your affected arm using surface electrodes adhered to your skin. We aim to use TMS to collect several measures that will tell us about how the motor pathways are working and will compare the TMS measures to standard clinical tests of your function. You will be asked to gently contract your leg muscles at various times during the experiment while TMS measurements are taking place. You will be given rest periods as needed so your muscles don't get tired. If you experience any discomfort you can ask the experimenters to slow down the measure or stop.

Summary of procedures

TMS assessments and clinical tests will be made by the chief investigator (Brenton Hordacre). The clinical tests will assess your functional ability and will include mobility and balance assessments and a gait analysis investigating muscle function during walking. A questionnaire will be used to determine how much pain you experience as an amputee. All the procedures will take place in the Rehabilitation Centre at Repatriation General Hospital.

You will undergo one session of TMS measures and session clinical assessments on the same day. The questionnaire and clinical assessments will take approximately 1.5 hours and the TMS measures will take approximately 1.5 hours.

Commitments

The collection of clinical and laboratory information will total no more than 3 hours and will be conducted on a single day. All assessments and treatments will be conducted on site at the Repatriation General Hospital. Reimbursement is available for parking and travel expenses incurred as a result of participation in this study.

Benefits

It is not anticipated you will directly benefit from participating in this study. It is hoped that outcomes of this trial will lead to further and larger studies designed to maximize recovery in the future. Data collected may improve current clinical practice and this will benefit future patients who have experienced lower limb amputation.

Risks and adverse effects

TMS is painless and safe and has few side effects when delivered according to established protocols. We will ensure it is safe for you to have TMS before starting the trial by using a screening questionnaire that will be reviewed by a hospital physician. The coil is held gently over the scalp and there is no need to shave the hair on your head. When coil discharges it makes an audible 'click'. This is not loud enough to affect your hearing, but if it is a nuisance to you we can provide you with an earplug.

We will record the electrical activity of your thigh muscles on both of your legs. This electrical activity will be recorded by electrodes positioned over the muscles of interest. The skin must first be prepared by shaving hair and mild abrasion of the skin. This can result in a mild and transient irritation of the skin that does not require treatment. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the TMS coil. Epileptic seizures have also been reported both during TMS and shortly after stimulation has ceased. However, induction of seizures as a result of TMS is considered to be rare. An extensive safety questionnaire will be performed to assess those patients deemed at risk of adverse effects. The questionnaire aims to exclude persons with a high risk of having seizures with TMS but despite this,

there is a rare chance that a seizure may still occur. If in the rare event a seizure does occur, this may have implications for your occupation or vehicle license.

If you feel uncomfortable at any time during the experiment, please notify the experimenter. There are no other specific risks associated with the procedures and the equipment used in the study.

Compensation

If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is not automatic and you may have to take legal action to determine whether you should be paid.

Confidentiality

Under Australian privacy law all information collected about you must be kept confidential, unless you agree to it being released. If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities and by authorised people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentiality to you as a research participant and no information that could identify you will be given to anyone else. If the results of this study are published, for example in scientific journals, you will not be identified by name.

Records and data about your participation in this study may be used for study purposes, to obtain regulatory approval for the study or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.

Publication

It is the intention of the researchers that project outcomes will be published in conference papers, journals or other venues as appropriate and will form part of

a PhD thesis. You will not be identifiable in any publication or results of this study.

Withdrawal

Your participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in this study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive.

Outcomes

The results will be published in scientific journals. If you would like to be informed of the outcomes of the study you may leave your contact details with the researchers who will send you a letter in due course.

Expenses and payments

You will not receive any payment for participation in this study apart from compensation for any required reasonable travel costs and parking expenses for visits made during the study.

Contact

Should you require further details about the study at any time please contact Brenton Hordacre on (08) 8275 2835 or 0422056018.

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 6453 or email research.ethics@health.sa.gov.au

Appendix 10

Consent to Participation in Research

An Investigation into Rehabilitaiton of Recent Amputees: a pilot study

I, ...

(first or given names) (last name)

request and give consent to my involvement in the research project: Neurophysiology of recent amputees: a pilot study

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....

(first or given names) (last name)

and my consent is given voluntarily.

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I acknowledge that the details of the following has been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

I understand that:

1. As an amputee participant, I will attend weekly session whilst completing rehabilitation as an inpatient and fortnightly sessions as an outpatient in the Applied Brain Research Laboratory, lasting no more than 2.5 hours per sessions at the Repatriation General Hospital.

2. As a healthy control participant, I will attend a single session of TMS measures which is expected to last no more than 1.5 hours.
3. The assessments are a questionnaire and functional ability tests (amputee participants only) and Transcranial Magnetic Stimulation (TMS) measures.
4. TMS involves the application of magnetic stimulation to the brain.
5. My safety for TMS has been assessed using the participant safety questionnaire, signed by a hospital physician.
6. In the unlikely occurrence of an adverse event such as a seizure, medical support is available onsite at the Repatriation General Hospital.
7. I will participate in this study investigating recent amputees undertaking rehabilitation and healthy adults.

I have understood and I am satisfied with the explanations that I have been given.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant: .....

Date: .....

I,..... have described to .....

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: .....

Date: .....

Status in Project: .....

Appendix 11

Participant Information Sheet

An Investigation into Rehabilitaiton of Recent Amputees: a pilot study

Researchers

Brenton Hordacre

Dr Lynley Bradnam

Prof Maria Crotty

Invitation to participate

We would like to invite you to participate in this preliminary pilot trial investigating how changes in the human brain following amputation may influence an amputee's ability to function in the community effectively. Involvement in the pilot trial is completely voluntary, and entirely your choice. Whether you take part or not, your decision will not affect your medical care if you are currently receiving any with the health service at Repatriation General Hospital in any way.

Selection

You are eligible for this trial because you have either recently had a lower limb amputation and have been admitted for rehabilitation, or alternatively, you are considered a healthy participant and will be used as a comparison in this study. Your eligibility will be further determined following completion of a safety questionnaire relating to the equipment that will be used in the study. For example, you may not be eligible if you have a history of seizures, or have metal implants or fragments above the level of the shoulders. This is because there is a rare chance that the equipment - Transcranial Magnetic Stimulation (TMS), can induce seizures or cause metallic objects to move in the body.

Aims of the project

This pilot study aims to assess brain reorganisation that occurs following limb amputation in recent lower limb amputees. It will also investigate the relationship between the brain reorganisation and functional walking and balance measures, and how these change over the rehabilitation process. We intend to use this pilot study to gather information upon which a separate, larger study may be conducted at a later date.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and safe method to assess activity of brain signals sent to muscles around the body and is used extensively around the world to study movement disorders. TMS involves a brief magnetic pulse applied over the area of your brain controlling the muscles of your leg, through a coil placed lightly on the scalp. Recordings are made from the muscles above the knee joint of both legs using surface electrodes adhered to your skin. We aim to use TMS to collect several measures that will tell us about how the brain signals sent to muscles above the knee are working and will compare the TMS measures to standard clinical tests of your function. You will be asked to gently contract your leg muscles at various times during the experiment while TMS measurements are taking place. You will be given rest periods as needed so your muscles don't get tired. If you experience any discomfort you can ask the experimenters to slow down the measure or stop.

Summary of procedures

TMS assessments and clinical tests will be made by the chief investigator (Brenton Hordacre). The clinical tests will only be conducted on amputee participants and will assess your functional ability and will include walking and balance assessments. Amputee participants will also be asked to complete a short questionnaire related to pain. All the procedures will take place in the Rehabilitation Centre at Repatriation General Hospital.

If you are an amputee participant, you will undergo one session of TMS, clinical assessments and a pain questionnaire per week when completing rehabilitation as a patient staying within the hospital, and one session of TMS, clinical assessments and a pain questionnaire per fortnight when completing rehabilitation as a patient staying in the community. If you are a 'healthy participant', you will undergo a single session of TMS measures. This procedure will involve taking readings from muscles above the knee of

your amputated and non-amputated limb using electrode pads which stick to the skin surface. The TMS measures will take no more than 1.5 hours and the clinical assessments will take no more than 1 hour.

Commitments

The collection of information will range from 1.5 to 2.5 hours for each session depending on the number of functional assessments that you will be able to complete. The number of sessions you will be required for will depend on the duration of your rehabilitation program. All assessments and treatments will be conducted on site at the Repatriation General Hospital.

Benefits

It is not anticipated you will directly benefit from participating in this study. It is hoped that outcomes of this pilot study will lead to further and larger studies designed to maximize recovery in the future. Data collected may improve current clinical practice and this will benefit future patients who experience a lower limb amputation.

Risks and adverse effects

TMS is painless and safe and has few adverse events when delivered according to established protocols. We will ensure it is safe for you to have TMS before starting the study by using a screening questionnaire that will be reviewed by a hospital physician. The coil is held gently over the scalp and there is no need to shave the hair on your head. When the coil discharges it makes an audible 'click'. This is not loud enough to affect your hearing, but if it is a nuisance to you we can provide you with an earplug.

We will record the electrical activity of your thigh muscles on both of your legs. This electrical activity will be recorded by electrodes positioned over the muscles of interest. The skin must first be prepared by shaving hair and mild abrasion of the skin. This can result in a mild and transient irritation of the skin that does not require treatment. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the TMS coil. Epileptic seizures have also been reported both during TMS and shortly after stimulation has ceased. However, induction of seizures as a result of TMS is considered to be rare. An extensive safety questionnaire will be performed to assess those patients deemed at risk of adverse effects. The questionnaire aims

to exclude persons with a high risk of having seizures with TMS but despite this, there is a rare chance that a seizure may still occur. If in the rare event a seizure does occur, this may have implications for your occupation or vehicle license.

If you feel uncomfortable at any time during the experiment, please notify the experimenter. There are no other specific risks associated with the procedures and the equipment used in the study.

Compensation

If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is not automatic and you may have to take legal action to determine whether you should be paid.

Confidentiality

Under Australian privacy law all information collected about you must be kept confidential, unless you agree to it being released. If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities and by authorised people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentiality to you as a research participant and no information that could identify you will be given to anyone else. If the results of this study are published, for example in scientific journals, you will not be identified by name.

Records and data about your participation in this study may be used for study purposes, to obtain regulatory approval for the study or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.

Publication

It is the intention of the researchers that project outcomes will be published in conference papers, journals or other venues as appropriate and will form part of a PhD thesis. You will not be identifiable in any publication or results of this study.

Withdrawal

Your participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in this study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive.

Outcomes

The results will be published in scientific journals. If you would like to be informed of the outcomes of the study you may leave your contact details with the researchers who will send you a letter in due course.

Expenses and payments

You will not receive any payment for participation in this study apart from compensation for any required reasonable travel or parking costs for visits made during the study that would otherwise not have been required as part of your rehabilitation.

Contact

Should you require further details about the study at any time please contact Brenton Hordacre on (08) 8275 2835 or 0422056018.

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 6453 or email research.ethics@health.sa.gov.au

Appendix 12

Consent to Participation in Research

An Investigation into Rehabilitaiton of Recent Amputees

I, ...

(first or given names) (last name)

request and give consent to my involvement in the research project: Neuroplasticity in transtibial amputees following amputation.

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

.....

(first or given names) (last name)

and my consent is given voluntarily.

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I acknowledge that the details of the following has been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

I understand that:

1. I will attend up to 2 sessions prior to my amputation, and up to 6 sessions following my amputation at the Repatriation General Hospital.
2. Each session duration is no longer than 2.5 hours.
3. The assessments are functional tests and Transcranial Magnetic Stimulation (TMS) measures.

4. TMS involves the application of magnetic stimulation to the brain.
5. My safety for TMS has been assessed using the participant safety questionnaire, signed by a hospital physician.
6. In the unlikely occurrence of an adverse event such as a seizure, medical support is available onsite at the Repatriation General Hospital.
7. I will participate in this study investigating recent amputees undertaking rehabilitation.

I have understood and I am satisfied with the explanations that I have been given.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant: .....

Date: .....

I,..... have described to .....

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: .....

Date: .....

Status in Project: .....

Appendix 13

Participant Information Sheet

Investigation into Rehabilitaiton of Recent Amputees

Researchers

Brenton Hordacre

Dr Lynley Bradnam

Prof Maria Crotty

Invitation to participate

We would like to invite you to participate in this trial investigating how the human brain changes following amputation. Involvement in the trial is completely voluntary, and entirely your choice. Whether you take part or not, your decision will not affect your medical care if you are currently receiving any with the health service at Repatriation General Hospital in any way.

Selection

You are eligible for this trial as you are scheduled to have a lower limb amputation and subsequently be admitted for rehabilitation at the Repatriation General Hospital. Your eligibility will be further determined following completion of a safety questionnaire relating to the equipment that will be used in the study. For example, you may not be eligible if you have a history of seizures, or have metal implants or fragments above the level of the shoulders. This is because there is a rare chance that equipment - Transcranial Magnetic Stimulation (TMS) can induce seizures or cause metallic objects to move in the body.

Aims of the project

The study aims to assess how the human brain changes following lower limb amputation using TMS.

TMS is a non-invasive, painless and safe method to assess activity in the brain signals sent to muscles around the body, and is used extensively around the world to study movement disorders. TMS involves a brief magnetic pulse applied over the area of your brain controlling the muscles of your leg, through a coil placed lightly on the scalp. Recordings are made from the muscles above the knee joint of both legs using surface electrodes adhered to your skin. We aim to use TMS to collect several measures that will tell us about how the brain signals sent to muscles around the body are working and how they change as a result of the amputation. You will be asked to gently contract your leg muscles at various times during the experiment while TMS measurements are taking place. You will be given rest periods as needed so your muscles don't get tired, and if you experience any discomfort you can ask the experimenters to slow down the measures or stop.

Summary of procedures

TMS assessments and clinical tests will be made by the chief investigator (Brenton Hordacre). All the procedures will take place in the Rehabilitation Centre at Repatriation General Hospital.

You will undergo no more than two sessions of TMS prior to your scheduled amputation, and no more than six sessions following the amputation. It is expected that the TMS measures will take no more than 1.5 hours.

Commitments

As part of this study, you will be required to attend no more than eight TMS sessions of 1.5 hours duration. All assessments and treatments will be conducted on site at the Repatriation General Hospital.

Benefits

It is not anticipated you will directly benefit from participating in this study. It is hoped that outcomes of this study will lead to further and larger studies

designed to maximize recovery in the future. Data collected may improve current clinical practice and this will benefit future patients who experience a lower limb amputation.

Risks and adverse effects

TMS is painless and safe and has few adverse events when delivered according to established protocols. We will ensure it is safe for you to have TMS before starting the study by using a screening questionnaire that will be reviewed by a hospital physician. The coil is held gently over the scalp and there is no need to shave the hair on your head. When coil discharges it makes an audible 'click'. This is not loud enough to affect your hearing, but if it is a nuisance to you we can provide you with an earplug.

We will record the electrical activity of your thigh muscles on both of your legs. This electrical activity will be recorded by electrodes positioned over the muscles of interest. The skin must first be prepared by shaving hair and mild abrasion of the skin. This can result in a mild and transient irritation of the skin that does not require treatment. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the TMS coil. Epileptic seizures have also been reported both during TMS and shortly after stimulation has ceased. However, induction of seizures as a result of TMS is considered to be rare. An extensive safety questionnaire will be performed to assess those patients deemed at risk of adverse effects. The questionnaire aims to exclude persons with a high risk of having seizures with TMS but despite this, there is a rare chance that a seizure may still occur. If in the rare event a seizure does occur, this may have implications for your occupation or vehicle license.

If you feel uncomfortable at any time during the experiment, please notify the experimenter. There are no other specific risks associated with the procedures and the equipment used in the study.

Compensation

If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is

not automatic and you may have to take legal action to determine whether you should be paid.

Confidentiality

Under Australian privacy law all information collected about you must be kept confidential, unless you agree to it being released. If you consent to take part in this study, your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities and by authorised people from the hospital to check that the study is being carried out correctly. All these people will have a duty of confidentiality to you as a research participant and no information that could identify you will be given to anyone else. If the results of this study are published, for example in scientific journals, you will not be identified by name.

Records and data about your participation in this study may be used for study purposes, to obtain regulatory approval for the study or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.

Publication

It is the intention of the researchers that project outcomes will be published in conference papers, journals or other venues as appropriate and will form part of a PhD thesis. You will not be identifiable in any publication or results of this study.

Withdrawal

Your participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in this study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive.

Outcomes

The results will be published in scientific journals. If you would like to be informed of the outcomes of the study you may leave your contact details with the researchers who will send you a letter in due course.

Expenses and payments

You will not receive any payment for participation in this study apart from compensation for any required reasonable travel or parking costs for visits made during the study that would otherwise not have been required as part of your rehabilitation.

Contact

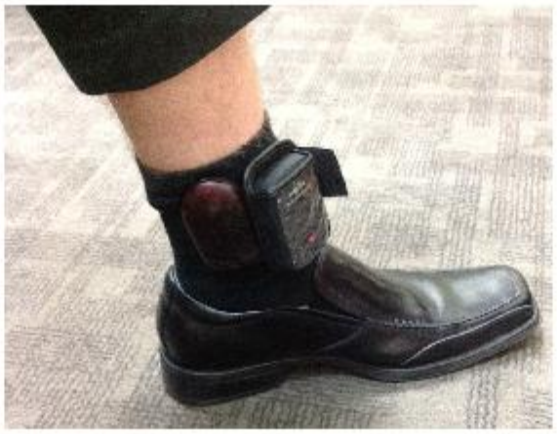
Should you require further details about the study at any time please contact Brenton Hordacre on (08) 8275 2835 or 0422056018.

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 6453 or email research.ethics@health.sa.gov.au

Appendix 14

Information About The GPS Unit

1. As part of the study investigating community ambulation of lower limb amputees you have been provided with a GPS unit and charging device (pictured right)



2. The GPS unit will be attached to your prosthesis along with a step activity monitor (SAM). You should not need to remove either of these units during the study. They will be attached together (and may be taped in place).

3. The GPS unit will require charging of the battery daily. The unit can be charged overnight whilst you are sleeping. Simply connect the charging device to the side of the GPS unit

In the morning, you can disconnect the charging device and wear the prosthesis with attached GPS and step activity monitor as normal.

We greatly appreciate the assistance of all participants who have volunteered their time to be participants in this study.

Frequently Asked Questions

1. I am unsure if the GPS unit is charging correctly

   When charging, a green battery symbol should appear to the right of the red button on the front of the GPS unit. You will also notice a red light appearing on the wall plug unit.

2. How do I know if the battery is fully charged?

   When the battery is fully charged, the green battery symbol on the GPS unit stops appearing, and the red light on the wall plug unit changes to a green light.

3. How long should it take to charge the battery?

   Approximately 3 hours.

4. I have plugged the device in for charging, but there are no lights appearing on the GPS unit to indicate that it is charging.

   Check the connection between the charging lead and the GPS unit, and the charging lead and the wall plug unit to ensure that power can get to the GPS unit.

5. Why does the yellow light above the red button flash sometimes and not others?

   A flashing yellow light indicates that the GPS unit has found satellites and is able to log data. A non-flashing yellow light indicates that the GPS unit currently does not have any satellites in view.

6. What does the 'Log/Nav/Off' slide switch mean? Do I have to use it?

   The first time you come in to have the GPS unit attached, the researcher should set the unit to 'Log'. You should not need to change this at all for the duration of the study. If you notice the device is not set to 'Log' as the unit was bumped or knocked, please change it back to 'Log'.

7. Do I have to take the GPS unit out of the pouch to charge it?

   You should not have to remove the unit from the pouch to attach it to the charging device.

8. I forgot to charge the device overnight—what should I do?

   The battery life of the device is approximately 40hrs, and the battery therefore should have enough power if charging is forgotten one night. However, to help ensure that data is not missed, we recommend charging the device each night.

9. Is the device waterproof? Can I wear it in the shower?

   The GPS unit is <u>not</u> waterproof and should be removed before showering or participating in any water related activities.

If you have further concerns which have not been addressed here, please do not hesitate to contact **Brenton Hordacre** on **0422056018 or (08) 82752835**.

Appendix 15

Applied Brain Research Laboratory

Screening Questionnaire for Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

Last Name_____

First Name_____

Please take the time to answer the following questions.	Yes	No
1. Do you have epilepsy or have you ever had a convulsion or seizure?	☐	☐
2. Does anyone in your family suffer from epilepsy?	☐	☐
3. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s). _____ _____	☐	☐
4. Have you ever had a head trauma that was diagnosed as concussion or was associated with loss of consciousness or a serious head injury?	☐	☐
5. Do you suffer from recurring headaches?	☐	☐
6. Have you ever had any head or brain surgery?	☐	☐
7. Do you have any hearing problems or ringing in your ears?	☐	☐
8. Do you have cochlear implants?	☐	☐

9. Are you pregnant or is there any chance you might be? ☐ ☐

10. Do you have metal in the brain, skull or elsewhere in your body (e.g. splinters, fragments, clips, etc) except titanium? ☐ ☐

11. Do you have an implanted neurostimulator (e.g. DBS, epidural/subdural,VNS)? ☐ ☐

12. Do you have a cardiac pacemaker or intracardiac lines or a medical infusion device? ☐ ☐

13. Do you, or have you ever suffered from a sleep disorder? ☐ ☐

14. Do you suffer from heart disease or had heart surgery? ☐ ☐

15. Are you taking any medications? (please list on next page) ☐ ☐

16. Have you had any other brain-related condition or illness that caused brain injury? ☐ ☐

17. Do you suffer from any neurological or other medical conditions? ☐ ☐

18. Did you ever undergo TMS in the past? If so, were there any problems? ☐ ☐

_____

_____

19. Did you ever undergo MRI in the past? If so, were there any problems? ☐ ☐

_____

_____

Please indicate if you are currently taking any of the following medications and your current dosage.

Medication (generic)	Medication (brand or tradename)	Currently on this medication (please tick)	Current Dosage
Amantadine	Symmetrel®	☐	_____
Alprazolam	Xanax®	☐	_____
Baclofen	Pacifen®	☐	_____
Benztropine	Benztrop® (tab) Cogentin® (injection)	☐	_____
Carbamazepine	Tegretol® Teril®	☐	_____
Citalopram	Celapram® Arrow-citalopram® Citalopram-Rex® Cipramil®	☐	_____
Clobazam	Frisium®	☐	_____
Clonazepam	Rivitril® (oral drops & injection) Paxam® (oral)	☐	_____
Fluoxetine	Fluox® Prozac®	☐	_____
Gabapentin	Neurontin® Nupentin®	☐	_____
Haloperidol	Haldol® (injection) Serenace®	☐	_____
Hyoscine	Scopaderm® (patch) Buscopan®	☐	_____
Ketamine		☐	_____

Lamotrigine	Lamictal® Arrow-lamotrigine® Mogine®	☐	_____
Levodopa + benserazide	Madopar®	☐	_____
Levodopa + carbidopa	Sinemet®	☐	_____
Lisuride	Dopergin®	☐	_____
Lorazepam	Ativan® Lorapram®	☐	_____
Mirtazapine	Remeron® Avanza® Zispin®	☐	_____
Methylphenidate	Ritalin®	☐	_____
Moclobemide	Apo-moclobemide® Aurorix®	☐	_____
Paroxetine	Loxamine® Aropax®	☐	_____
Pergolide	Permax®	☐	_____
Phenytoin	Dilantin®	☐	_____
Quetiapine	Seroque® Quetapel®	☐	_____
Selegiline	Apo-selegiline® Eldepryl®	☐	_____
Sertraline	Zoloft®	☐	_____
Sodium valproate	Epilim®	☐	_____
Temazepam	Normison® Euhypnos®	☐	_____
Tolcapone	Tasmar®	☐	_____
Topiramate	Topamax®	☐	_____

Triazolam	Hypam® Halcion®	☐	_____
Venlafaxine	Efexor®	☐	_____
Vigabatrin	Sabril®	☐	_____

Please list any additional medications, including the dose.

_____

_____

_____

_____

_____

_____

_____

_____

Please outline any neurological or medical conditions you have.

_____

_____

_____

_____

_____

_____

_____

_____

Participant	Researcher
Name:_____	Name:_____
Signature:_____	Signature:_____
Date:_____	Date:_____

Other information:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Include ☐ Exclude ☐

Study Physician_____	Researcher _____
Signed_____	Signed_____
Date_____	Date_____

Name:_____ Name:_____

Signature:_____ Signature:_____

Date:_____ Date:_____

Name:_____ Name:_____

Signature:_____ Signature:_____

Date:_____ Date:_____

Name:_____ Name:_____

Signature:_____ Signature:_____

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Name:_____ Name:_____

Signature:_____ Signature:_____

Date:_____ Date:_____

Name:_____ Name:_____

Signature:_____ Signature:_____

Date:_____ Date:_____

Appendix 16

EDINBURGH HANDEDNESS INVENTORY

Last name: _____

First names: _____

Date of birth: _____ Gender: _____

Please indicate your preference for the use of the left or right hand in the following tasks by placing a "+" in the appropriate column. If you have such a strong preference for one hand that you would never try to use the other unless forced to, place a "++" in the column. If you would perform the task with either hand place a "+" in both columns.

Some of the tasks require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in the brackets.

Please try to answer all of the questions. Only leave a blank if you have no experience of the task or object.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking match (match)		
10	Opening box (lid)		
I	Which foot do you prefer to kick with?		
II	Which eye do you use when only using one?		

Appendix 17

AMPUTEE MOBILITY PREDICTOR ASSESSMENT TOOL

Initial instructions: Client is seated in a hard chair with arms. The following manoeuvres are tested with or without the use of the prosthesis. Advise the person of each task or group of tasks prior to performance. Please avoid unnecessary chatter throughout the test. Safety First, no task should be performed if either the tester or client is uncertain of a safe outcome.

The **Right Limb** is: ❒ PF ❒ TT ❒ KD ❒ TF ❒ HD ❒ intact

The **Left Limb** is: ❒ PF ❒ TT ❒ KD ❒ TF ❒ HD ❒ intact

1. Sitting Balance: Sit forward in a chair with arms folded across chest for 60s.	Cannot sit upright independently for 60s Can sit upright independently for 60s	= 0 = 1	_____
2. Sitting reach: Reach forwards and grasp the ruler. (Tester holds ruler 12in beyond extended arms midline to the sternum)	Does not attempt Cannot grasp or requires arm support Reaches forward and successfully grasps item.	= 0 = 1 = 2	_____
3. Chair to chair transfer: 2 chairs at 90°. Pt. may choose direction and use their upper limbs.	Cannot do or requires physical assistance Performs independently, but appears unsteady Performs independently, appears to be steady and safe	= 0 = 1 = 2	_____
4. Arises from a chair: Ask pt. to fold arms across chest and stand. If unable, use arms or assistive device.	Unable without help (physical assistance) Able, uses arms/assist device to help Able, without using arms	= 0 = 1 = 2	_____

5. Attempts to arise from a chair: (stopwatch ready) If attempt in no. 4. was without arms then ignore and allow another attempt without penalty.	Unable without help (physical assistance) Able requires >1 attempt Able to rise one attempt	= 0 = 1 = 2	_____
6. Immediate Standing Balance: (**first 5s**) Begin timing immediately.	Unsteady (staggers, moves foot, sways) Steady using walking aid or other support Steady without walker or other support	= 0 = 1 = 2	_____
7. Standing Balance (30s): (stopwatch ready) For item no.'s 7 & 8, first attempt is without assistive device. If support is required allow after first attempt	Unsteady Steady but uses walking aid or other support Standing without support	= 0 = 1 = 2	_____
8. **Single limb standing balance:** **(stopwatch ready) Time the duration of single limb standing on both the sound and prosthetic limb up to 30s.** **Grade the quality, not the time.** ***Eliminate item 8 for AMPnoPRO**** Sound side _____ seconds Prosthetic side _____ seconds	**Non-prosthetic side** Unsteady Steady but uses walking aid or other support for 30s Single-limb standing without support for 30s **Prosthetic Side** Unsteady Steady but uses walking aid or other support for 30s Single-limb standing without support for 30s	= 0 = 1 = 2 = 0 = 1 = 2	_____ _____
9. Standing reach: Reach forward and grasp the ruler. (Tester holds ruler 12in beyond extended arm(s) midline to the sternum)	Does not attempt Cannot grasp or requires arm support on assistive device Reaches forward and successfully grasps item no support	= 0 = 1 = 2	_____
10. Nudge test: With feet as close together as possible, examiner pushes lightly	Begins to fall Staggers, grabs, catches self ore uses assistive	= 0 = 1	

on pt.'s sternum with palm of hand 3 times (toes should rise)	device Steady	= 2	_____
11. Eyes Closed: (at maximum position #7) If support is required grade as unsteady.	Unsteady or grips assistive device Steady without any use of assistive device	= 0 = 1	_____
12. Pick up objects off the floor: Pick up a pencil off the floor placed midline 12in in front of foot.	Unable to pick up object and return to standing Performs with some help (table, chair, walking aid etc) Performs independently (without help)	= 0 = 1 = 2	_____
13. Sitting down: Ask pt. to fold arms across chest and sit. If unable, use arm or assistive device.	Unsafe (misjudged distance, falls into chair) Uses arms, assistive device or not a smooth motion Safe, smooth motion	= 0 = 1 = 2	_____
14. Initiation of gait: (immediately after told to "go")	Any hesitancy or multiple attempts to start No hesitancy	= 0 = 1	_____
15. Step length and height: Walk a measured distance of 12ft twice (up and back). Four scores are required or two scores (a. & b.) for each leg. "Marked deviation" is defined as extreme substitute movements to avoid clearing the floor.	**a. Swing Foot** Does not advance a minimum of 12in Advances a minimum of 12in **b. Foot Clearance** Foot does not completely clear floor without deviation Foot completely clears floor without marked deviation	 = 0 = 1 = 0 = 1	Prosthesis _____ _____	Sound _____ _____
16. Step Continuity	Stopping or discontinuity between steps (stop & go gait) Steps appear continuous	= 0 = 1	_____
17. Turning: 180 degree turn when returning to chair.	Unable to turn, requires intervention to prevent falling Greater than three steps but completes task without intervention	= 0 = 1	

	No more than three continuous steps with or without assistive aid	= 2	_____
18. Variable cadence: Walk a distance of 12ft fast as possible safely 4 times. (Speeds may vary from slow to fast and fast to slow varying cadence)	Unable to vary cadence in a controlled manner Asymmetrical increase in cadence controlled manner Symmetrical increase in speed in a controlled manner	= 0 = 1 = 2	_____
19. Stepping over an obstacle: Place a movable box of 4in in height in the walking path.	Cannot step over the box Catches foot, interrupts stride Steps over without interrupting stride	= 0 = 1 = 2	_____
20. Stairs (must have at least 2 steps): Try to go up and down these stairs without holding on to the railing. Don't hesitate to permit pt. to hold on to rail. Safety First, if examiner feels that any risk in involved omit and score as 0.	**Ascending** Unsteady, cannot do One step at a time, or must hold on to railing or device Step over step, does not hold onto the railing or device **Descending** Unsteady, cannot do One step at a time, or must hold on to railing or device Step over step, does not hold onto the railing or device	= 0 = 1 = 2 = 0 = 1 = 2	_____ _____
21. Assistive device selection: Add points for the use of an assistive device if used for two or more items. If testing without prosthesis use of appropriate assistive device is mandatory.	Bed bound Wheelchair / Parallel Bars Walker Crutches (axillary or forearm) **Cane (straight or quad)** None	= 0 = 1 = 2 = 3 = 4 = 5	_____

Total Score	AMPnoPRO _____/43 AMPPRO _____/47

Abbreviation: PF = partial foot; TT = transtibial; KD = knee disarticulation; TF = transfemoral; HD = hip disarticulation

Test: ☐ no prosthesis ☐ with prosthesis

Observer: _____ **Date:** _____

K LEVEL (converted from AMP score)

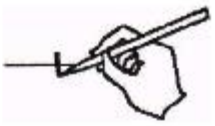
AMPnoPRO ☐ K0 (0-8) ☐ K1 (9-20) ☐ K2 (21-28) ☐ K3 (29-36) ☐ K4 (37-43)

AMPPRO ☐ K1 (15-26) ☐ K2 (27-36) ☐ K3 (37-42) ☐ K4 (43-47)

Appendix 18

Study Number _____
Date _____

Prosthesis Evaluation Questionnaire



Group 2

The next section covers very SPECIFIC BODILY SENSATIONS. Here are our definitions:

1. *SENSATIONS* are feelings like "pressure", "tickle" or a sense of position or location, such as the toes being curled. Amputees have described sensations in their missing (phantom) limb such as "the feeling that my (missing) foot is wrapped in cotton."

2. *PAIN* is a more extreme sensation described by terms such as "shooting", "searing", "stabbing", "sharp", or "ache".

3. *PHANTOM LIMB* refers to the part that is missing. People have reported feeling sensations and/or pain in the part of the limb that has been amputated — that is, in their phantom limb.

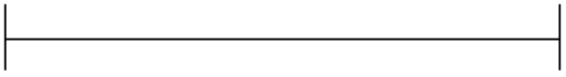
4. *RESIDUAL LIMB (STUMP)* refers to the portion of your amputated limb that is still physically present.

REGARDING SENSATIONS IN YOUR PHANTOM LIMB

A. Over the past four weeks, rate how often you have been aware of non-painful sensations in your phantom limb.

a. never
b. only once or twice
c. a few times (about once/week)
d. fairly often (2-3 times/week)
e. very often (4-6 times/week)
f. several times every day
g. ___ all the time or almost all the time

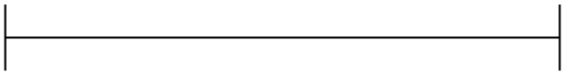
B. If you had non-painful sensations in your phantom limb during the past month, rate how intense they were on average.



EXTREMELY INTENSE EXTREMELY MILD

OR check ___ I did not have non-painful sensations in my phantom limb.

C. Over the past month, how bothersome were these sensations in your phantom limb?



ALL THE TIME NEVER

OR check I did not have non-painful sensations in my phantom limb.

REGARDING PAIN IN YOUR PHANTOM LIMB

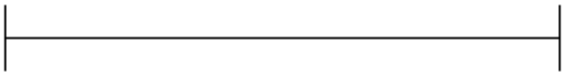
D. Over the past four weeks, rate how often you had pain in your phantom limb.

a. never
b. ___ only once or twice
c. a few times (about once/week)
d. fairly often (2-3 times/week)
e. very often (4-6 times/week)
f. several times every day
g. all the time or almost all the time

E. How long does your phantom limb pain usually last?

a. I have none
b. a few seconds
c. a few minutes
d. ___ several minutes to an hour
e. several hours
f. a day or two
g. more than two days

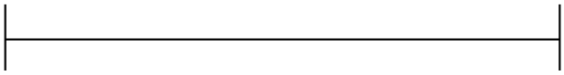
F. If you had any pain in your phantom limb this past month, rate how intense it was on average.



EXTREMELY INTENSE EXTREMELY MILD

OR check I did not have any pain in my phantom limb.

G. In the past four weeks how bothersome was the pain in your phantom limb?



EXTREMELY BOTHERSOME EXTREMELY MILD

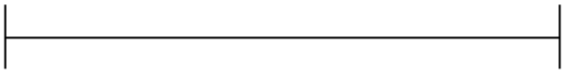
OR check_____ I did not have any pain in my phantom limb.

REGARDING PAIN IN YOUR RESIDUAL LIMB (STUMP)

H. Over the past four weeks, rate how often you had pain in your residual limb.

a. ___ never
b. ___ only once or twice
c. ___ a few times (about once/week)
d. fairly often (2-3 times/week)
e. very often (4-6 times/week)
f. several times every day
g. ___ all the time or almost all the time

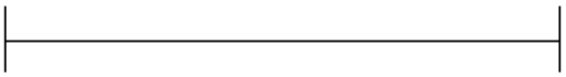
I. If you had any pain in your residual limb over the past four weeks, rate how intense it was on average.



EXTREMELY INTENSE EXTREMELY MILD

OR check ___ I did not have any pain in my residual limb.

J. OVER THE past four weeks how bothersome was the pain in your residual limb?



EXTREMELY BOTHERSOME NOT AT ALL

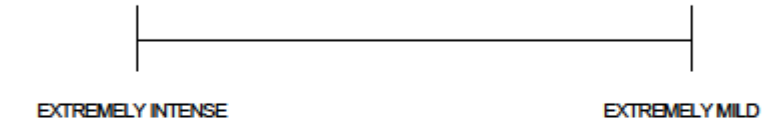
OR check I did not have any pain in my residual limb.

REGARDING PAIN IN YOUR OTHER (NON-AMPUTATED) LEG OR FOOT

K. Over the past four weeks, rate how often you had pain in your other leg or foot.

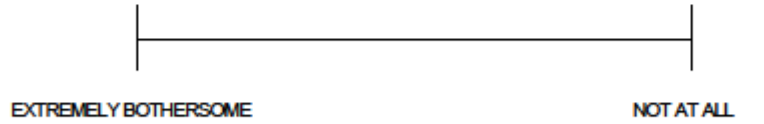
a. never
b. ___ only once or twice
c. ___ a few times (about once/week)
d. ___ fairly often (2-3 times/week)
e. ___ very often (4-6 times/week)
f. ___ several times every day
g. all the time or almost all the time

L. **If you had any pain in your other leg or foot over the past four weeks, rate how intense it was on average.**



OR check ___ I had no pain in my other leg or foot.

M. **OVER THE past four weeks how bothersome was the pain in your other leg or foot?**



OR check ___ I had no pain in my other leg or foot.

REGARDING BACK PAIN

N. **Over the past four weeks, rate how often you experienced back pain.**

a. ___ never
b. ___ only once or twice
c. ___ a few times (about once/week)
d. ___ fairly often (2-3 times/week)
e. ___ very often (4-6 times/week)
f. ___ several times every day
g. all the time or almost all the tune

O. **If you had any back pain over the past four weeks, rate how intense it was on average.**

OR check I had no back pain.

