University of Brighton

The role of the prefrontal cortex in the control of dual-task gait

James Graeme Wrightson

A thesis submitted in partial fulfilment of the requirements of the University of Brighton for the degree of Doctor of Philosophy

July 2016

University of Brighton

Sport and Service Management

Abstract

Prefrontal cortex is frequently linked to dual-task gait performance; however, its precise role is unknown. The purpose of this thesis was to examine the role of prefrontal cortex in the control of dual-task gait. Using transcranial direct stimulation (tDCS) to alter prefrontal cortex activity, the influence of prefrontal cortex on dual-task gait performance and the corticospinal system was examined across four experiential studies using the guided activation framework of prefrontal cortex function (Miller and Cohen, 2001).

The first study examined the role of cognitive task type and walking speed on stride time variability and trunk range of motion during dual-task walking. Results revealed the greatest dual-task cost on gait occurred when walking at a slow speed whilst simultaneously performing a serial subtraction task, compared to performance of a working memory task, providing a rationale for the use of this paradigm in later studies.

The second study examined the effect of prefrontal tDCS on dual-task gait performance during both normal and slow walking. Anodal tDCS reduced the dual-task cost on both gait and cognitive task performance, and these effects were not dependent on walking speed. These results indicating that prefrontal tDCS may alter the allocation of cognitive control across tasks during dual-task gait, in accordance with established models of prefrontal cortex function.

The third study examined the effect of prefrontal tDCS on corticospinal excitability and working memory performance. Results revealed that cathodal tDCS reduced corticospinal excitability. However, there was no effect of tDCS on working memory performance. Because prefrontal tDCS altered the activity in remote motor networks, these results indicated a possible mechanism by which prefrontal cortex exerts control over gait performance. In addition, because this study failed to replicate previous reports of working memory improvement following tDCS, these results also suggested a degree of inter-individual variability in response to tDCS.

The final study examined the influence of walking modality and task difficulty on the effects of prefrontal tDCS on dual-task gait performance. tDCS altered the allocation of cognitive control during over-ground dual-task gait performance, and these effects were mediated by task difficulty. In contrast to the second study, there was no effect of tDCS on treadmill dual-task gait. A secondary aim of the final study was to examine whether cognitive and walking task performance were coordinated. Results revealed that participants articulated answers during the initial swing phase of the gait cycle more frequently than other phases, indicating a degree of coordination between the performance of these tasks.

Overall the finding of this thesis indicate that prefrontal cortex is involved in the allocation of cognitive control processes during dual-task walking, in accordance with the guided activation and flexible hub accounts of frontal cortex function (Miller and Cohen, 2001; Cole et al., 2013). These findings may have implications for the design and validation of strategies aimed at improving the cognitive control of gait.

Table of Contents

Table of Figures

List of Tables

List of Equations

List of Abbreviations

ANOVA	Analysis of Variance
AP	Anterior-Posterior
cm	Centimetres
d	Cohen’s d Effect Size
deg	Degrees
EMG	Electromyography
EEG	Electroencephalogram
FDI	First dorsal interosseous
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near Infrared Spectroscopy
FPN	Fronto-Parietal network
h	Hours
Hz	Hertz
L5	Lumbar 5 Spinal segment
ICC	Intraclass correlation coefficient
km	Kilometres
m	Metres
MEP	Motor evoked potential
ML	Medio-Lateral
ms	Milliseconds
ηp	Partial eta Squared
RoM	Range of Motion
s	Seconds
SD	Standard Deviation
STV	Stride Time Variability
tDCS	Transcranial Direct Current Stimulation
TEM	Typical Error of the Measure
TMS	Transcranial Magnetic Stimulation

Acknowledgments

I would like to express my gratitude and appreciation to my supervisory team, Dr Peter Watt, Dr Emma Ross and Dr Nicholas Smeeton, without whose expertise, patience and resilience this thesis would not have been completed. I am sincerely grateful for all of your help.

Thank you to all of the academic staff at Brighton, particularly Dr Jeanne Derkele and Dr Martin Bailey, whose help and guidance has been invaluable. I would also like to thank my fellow University of Brighton postgraduate students, whose informal help, guidance and occasional counselling has kept me going throughout my studies.

I would like to acknowledge the technicians at the Welkin Human Performance Laboratories who assisted me during my studies, in particular Tom Howes without whom no science would have been done.

Finally, I would like to give my thanks to the Wrightsons. You helped me keep all this in perspective.

Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed

Dated

20/07/16

The following published articles have been due to work contained in this thesis:

Wrightson, J.G., Twomey, R., Ross, E.Z. and Smeeton, N.J., (2015). The effect of transcranial direct current stimulation on task processing and prioritisation during dual-task gait. *Experimental brain research*, 233(5), pp.1575–1583.

Wrightson, J.G., Twomey, R., Ross, E.Z. and Smeeton, N.J., (2015). Transcranial direct current stimulation (tDCS) of the prefrontal cortex influences task the allocation of attention during dual-task gait. *Brain stimulation*, 8(2), p.353.

Wrightson, J.G., Ross, E.Z. and Smeeton, N.J., (2016). The Effect of Cognitive Task Type and Walking Speed on Dual-Task Gait in Healthy Adults. *Motor control*, 20(1), pp.109–21.

1. Introduction

The population of the United Kingdom is aging, and it has been projected that by 2035 nearly 25% of all residents will be over 65 years old (Office for National Statistics, 2012). Up to 30% of older adults experience falls (American Geriatrics Society, 2001), and the majority of reported falls occur during walking (Li et al., 2006). Falls are a major cause of injury and mortality (Johnell and Kanis, 2005; Alamgir et al., 2012) and are estimated to cost the taxpayer £981 million per year (Scuffham, 2003). Understanding the cause of falls during locomotion in order to reduce fall-risk is thus a priority for researchers, clinicians and policy makers (American Geriatrics Society, 2001).

Bipedal locomotion places great demand on balance control systems: in order to move our centre of gravity forward, we essentially must initiate a fall which is only averted by the careful placement of the swinging foot (Winter, 1995). Consequently, the control of gait involves the co-ordination of a large number of muscular and neural processes (Winter, 1995). In addition to the well documented changes in physiology which predispose older adults to fall, there is increasing evidence that age related decline in cognitive function increases fall risk (Herman et al., 2010; Liu-Ambrose et al., 2008). The relationship between high-level cognitive functions and the control of gait is not fully understood; however, the ability to divide attention between multiple tasks during walking, for example to talk whilst walking (known as dual-task walking), has been shown to predict fall risk in older adults (Beauchet et al., 2009b). An increasing number of researchers have begun to examine the effect of cognitive enhancement interventions on dual-task gait and fall risk, however evidence for their efficacy is limited (Pichierri et al., 2011). Understanding the mechanisms which underpin the cognitive control of gait may help in the design of rehabilitation strategies that target this complicated multi-system process (Pichierri et al., 2011). Recent evidence has suggested that dual-task gait activates prefrontal cortex, a brain area linked to many high-level cognitive functions (Holtzer et al., 2011; Fuster, 2000). Prefrontal cortex undergoes significant structural and functional changes in old age (Dickstein et al., 2007). A prominent theory of age related cognitive decline, “ the frontal aging hypothesis” posits that age related changes to frontal cortex at least partially cause the well documented age related reductions in cognitive and gait performance (Wilson et al., 2002; West, 1996; Rosano et al., 2012).

Therefore, the aim of this thesis is to examine the role of prefrontal cortex in the control of dual-task gait. Chapter 2 reviews the pertinent dual-task gait, neuropsychological and brain stimulation literature. Chapter 3 describes the common methods used throughout this thesis. Chapter 4 examines the role of cognitive task type and walking speed on dual-task gait performance. Chapter 5 examines the effect of prefrontal tDCS on dual-task gait at two different walking speeds. Chapter 6 examines the effect of prefrontal tDCS on both cognitive task performance, and corticospinal excitability, in an attempt to reveal the functional mechanisms by which prefrontal cortex may influence dual-task performance. Chapter 7 compares the effects of prefrontal tDCS on dual-task gait in different walking modalities, and the coordination between task performance during dual-task walking. Chapter 8 discusses the results from the experimental chapters, and provides implications and applications of these findings.

2. Literature Review

The following section will provide a synopsis of the literature pertaining to dual-task gait performance, the proposed functions of prefrontal cortex, and use of tDCS to examine the neural correlates of behaviour. The first part describes the dual-task paradigm and current understanding of the causes of the dual-task effect. The second section outlines the neural mechanisms which underpin the control of gait, and will introduce the current understanding of the intersecting roles of prefrontal cortex and cognition in the control of dual-task gait. Subsequently the emerging field of transcranial direct current stimulation (tDCS), a method by which the neural correlates of behaviours such as dual-task gait can be examined, will be introduced. Finally, the aims and hypotheses of this thesis are presented.

2.1 Dual-Tasks and Dual-Task Gait

Humans frequently perform multiple tasks simultaneously. However, it has long been observed that during simultaneous performance of two or more tasks, performance on one or both of the tasks is impaired (James, 1890). Anecdotally, one might identify a number of multitask situations: talking on the telephone whilst driving, or typing a message on a mobile phone whilst walking for example. The limits of human multi-tasking ability has implications for a number of areas including work place and transport safety (Strayer and Johnston, 2001; Rosa et al., 1989) and in fall prevention and rehabilitation medicine (Lundin-Olsson et al., 1997). This ability to perform tasks simultaneously has been scientifically examined using dual-task paradigms. The following sections will outline the early dual-task paradigms and the models that were developed to explain their results. Subsequently, an ecologically valid model of dual-task performance, the dual-task gait paradigm, will be discussed.

2.1.1 Traditional Dual-Task Paradigms

Since the mid twentieth century two paradigms dominated research examining people's ability, or lack thereof, to multitask: the Psychological Refractory Period (PRP) and the Attentional Blink (AB) paradigms. The PRP paradigm examines the effect of two serially presented stimuli on reaction time (Welford, 1952). The two stimuli are presented sequentially and the time between stimuli (the stimulus onset asynchrony, SOA) is experimentally manipulated. Participants are required to respond to both stimuli. When the stimulus onset asynchrony, which is usually within the range of 50-1500ms, is reduced, reaction time to the second stimuli is increased. This is assumed to be caused by a limitation of the central processes required to react to the stimuli, whereby the central processes are unable to complete the reaction to the first stimuli in time to allow response to the second stimuli (Welford, 1952). Initially reported by Telford (1931), the existence of the PRP has been confirmed in a large number of studies since (e.g. Welford 1952; Smith 1967; Pashler 1990). In the AB paradigm, sequences of visual stimuli are presented in the same location on a screen in rapid succession, and the participant is required to react to all stimuli (Shapiro et al., 1997). The ability of an individual to correctly respond to the second stimuli is influenced by the lag between first and second stimuli (Raymond et al., 1992). As with the PRP, the assumption is that response to the first stimuli 'ties up' central resources, which make identification of the second stimuli more difficult (Shapiro et al., 1997).

Both the PRP and the AB examine the effect of serially presented tasks on task performance, and thus performance in these tasks may not be fully synonymous with the simultaneous performance of multiple tasks. Nonetheless, the ability to experimentally manipulate both the stimulus onset asynchrony and lag has allowed researchers to examine the central processes involved in dual-task performance. Using both the AB and PRP paradigms, a number of mechanisms for the dual-task effect have been suggested (Shapiro et al., 1997; Pashler, 1994).

2.1.2 The Dual-Task Effect: Mechanisms

The exact mechanisms which cause the dual-task effect continue to be debated. Three contrasting models have dominated dual-task research: the bottleneck, central capacity and cross-talk models.

2.1.2.1 The Bottleneck Model

The bottleneck model posits that dual-task costs occur because both tasks are trying to engage one central, limited, cognitive resource. This central resource operates serially, so concurrent demands on this resource leads to a bottleneck in processing. Importantly, it assumes that tasks cannot be processed concurrently. Pashler (1994) reported that the PRP occurred when tasks did not share input or output systems, suggesting that a bottleneck may occur later during response selection. Existence of a central bottleneck has been examined by manipulating the length of the SOA. A number of studies have shown that shortening the SOA between the first and second task leads to increases in the reaction time during task two performance, suggested to occur because task 1 still "occupies" the central resource bottleneck, and task 2 must wait for this to be cleared before it can "occupy" the same resource (Pashler and Johnston, 1989; Pashler, 1984). The bottleneck model predicts that task 2 performance (reaction time) will always be affected when performed a sufficiently short time after task 1. However, this is not always the case; there are negligible dual-task costs when participants are sufficiently practiced at the tasks (Van Selst et al., 1999). Whilst this might suggest that dual-tasks can be carried out simultaneously and rule out the existence of a central bottleneck, Ruthruff et al. (2003) instead proposed a latent bottleneck model, in which during well practiced tasks the bottleneck is too short for the manipulation of the SOA to capture. Another limitation of the bottleneck theory is that it predominantly describes the effects of serially performed dual-tasks. Though Pashler (1994) has suggested it can also be applied to continuously performed dual–tasks, there is a lack of experimental evidence supporting the model in these paradigms.

2.1.2.2 The Central Capacity Model

In the central capacity model, task performance is dependent on capacity limited pools of cognitive resources (Kahneman, 1973). In contrast to the bottleneck model, the central capacity model allows for parallel processing of tasks and presumes that capacity can be voluntarily allocated to tasks, even if the tasks are thought to be "automatic" (Abernethy, 1988; Wickens, 2002). Dual-task costs are suggested to occur if one of the concurrently performed tasks requires increased allocation of resources which exceeds the limited capacity of the system (Kahneman, 1973; Tombu and Jolicœur, 2003). Bourke and colleagues (1996) used four tasks which made different demands on cognitive processing. They reported that simultaneous performance of a random generation task with a learning task, a manual task or an auditory discrimination task led to greater impairment in secondary task performance than performance of any two of the other tasks together. Bourke et al. (1996) suggested that the random generation task placed greater demands on cognitive resources, and performance of this task resulted in a reduction in the shared cognitive resources available for secondary task performance. Whilst the capacity sharing model helps to explain situations where dual-task costs are negligible or even absent, and is easily applicable to simultaneous rather than serial dual-tasks, it does not define the nature of the central resource(s). Wickens' (2002) multiple resource model attempted to rectify this issue (Figure 1, below) by identifying several resource pools which are dependent on the stimulation modality (audio, visual, etc.) the processing stage and the response modality (verbal, manual, etc.). According to Wickens, dual-task costs will occur only if the two simultaneously performed tasks access the same resource pool, otherwise both tasks can be performed with no detriment to task performance.

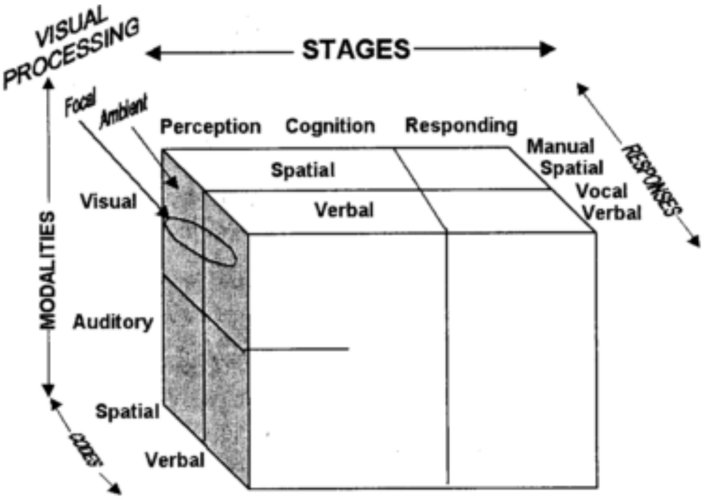

Figure 1. Wickens' (2002) multiple resource model. Extending existing capacity sharing models, Wickens' proposed distinct modality and stage dependent resources, competition for which causes dual-task effects.

2.1.2.3 The Cross-talk model

The cross-talk model posits that the dual-task effect occurs because of similarities in the information required for processing of both tasks such as stimulus type or output modality. In the cross-talk model, dual-task effects occur because parallel processing of the dual-tasks, which share informational properties, prevents the performer from separating the demands of each task, causing interference (Pashler, 1994). The cross-talk model differs from standard resource competition models by suggesting that the dual-task effect occurs because participants adopt a serial processing strategy in response to task interference (Navon and Miller, 1987, 2002).

2.1.2.4 A Limited Capacity Central Resource

The exact cause of the dual-task effect remains controversial, and is an ongoing topic of research (e.g. Han & Marois 2013). However, the common proposal amongst the relevant theories is that the engagement of a central cognitive resource by two or more simultaneously performed tasks leads to impaired performance in one or all of the tasks. In these models, it is widely assumed that the demands of both tasks are equal to the demands of both tasks when performed separately. This demand exceeds the capacity of the central cognitive systems required for task performance, and thus task performance is reduced. Based on this framework, dual-task paradigms have been employed to examine the role of central cognitive processes in the performance of a number of different motor tasks (Crossley et al., 2004; Perry et al., 2000). The assumption is that if simultaneous performance of both a motor and cognitive task impairs performance in one of both tasks, then the dual-task theories suggest that both tasks require access to the same resources (Woollacott and Shumway-Cook, 2002). Of relevance to this thesis is the use of the dual-task paradigm to examine the role of cognitive processing in the control of gait.

2.1.3 Dual-Task Gait

Gait was considered an automatic processes, which required very little input from high level cognitive systems (Woollacott and Shumway-Cook, 2002). However, at the end of the twentieth century a number of researchers reported that, rather than be considered an automatic task, gait required a degree of cognitive control. Using a dual-task gait paradigm, wherein the walker simultaneously performs a secondary cognitive task whilst walking, Lajoie et al., (1993) reported that performance in a verbal reaction time task decreased during walking, compared to standing and sitting. Lajoie and colleagues concluded that, because walking influenced performance in the secondary cognitive task, controlling posture and balance required input from the same high-level cognitive processes used for performance of the secondary task. Subsequently, Ebersbach et al. (1995) subsequently examined the effects of four different cognitive and motor tasks on dual-task gait performance. They reported that performance of a motor task (finger tapping) affected stride time whilst performance of a cognitive task (digit span) influenced double limb support time, suggesting that the control of temporal gait parameters was at least partially dependent on the same resources used for cognitive task performance.

These early results have been replicated in a number of studies in heathy adults (for e.g. Grabiner & Troy 2005; Beauchet et al. 2005; Szturm et al. 2013) all of which report changes to either gait or cognitive task performance during dual-task gait (see Al-Yahya et al., (2011) for a review). Under the established dual-task models, changes to gait and/or cognitive task performance during dual-task walking indicates that both tasks are competing for shared cognitive resources. Gait is therefore unlikely to be a solely automatic process, but instead requires some degree of cognitive control (Woollacott and Shumway-Cook, 2002).

Because gait performance requires cognitive control, then it is reasonable to assume that an individual's cognitive capacity would influence their dual-task walking performance. Indeed, a number of studies have reported a relationship between cognitive capacity and dual-task gait performance. Camicioli and colleagues (1997) reported that, compared to age matched controls, patients with Alzheimer's disease reduced walking speed significantly during dual-task gait. Subsequently, a number of studies have reported age and disease related differences in dual-task gait performance in older adults (e.g. Beauchet et al. 2003; Springer et al. 2006) and neurological patients (e.g. Brauer & Morris 2010; Allali et al. 2007). Because cognitive capacity and dual-task gait performance appear intrinsically linked, Montero-Odasso and colleagues (Montero-Odasso et al., 2012; Montero-Odasso and Hachinski, 2014) suggest that dual-task gait performance may be a useful indicator of age or disease related reductions in brain function and cognitive function.

Importantly, decrements in dual-task gait performance appear to be related to fall risk. In their now seminal dual-task gait study, Lundin-Olsson et al. (1997) reported that whether an elderly patient stopped walking whilst talking was predictive of whether they would fall in the following six months. Yamada et al. (2011) reported that changes in dual-task gait performance of 18% or over predicted fall risk [Odds Ratio: 1.07, 95% CI (1.04–1.10)] in a group of 1038 older adults. Cognitive impairment is also related to fall risk; decrements in high-level cognitive control processes predict falls in older adults [Odds Ratio: 1.44, 95% CI (1.20, 1.73)] (Muir et al., 2012). Whilst the mechanisms underpinning increased fall risk in cognitively impaired adults remains unclear, it is currently assumed that age and disease reduce an individual's ability to divide cognitive control processes over multiple tasks, i.e. reduce dual-task gait performance, resulting in decrements to gait performance and increased fall risk (Montero-Odasso et al., 2012). These findings have now been replicated across a range of different neurological and aged populations, and a number of systematic reviews now support the link between dual-task gait performance and fall risk (Beauchet et al., 2009b; Hsu et al., 2012; Muir-Hunter and Wittwer, 2016).

2.1.4 The Dual-Task Gait Paradigm

The relationship between dual-task gait performance and fall risk, and their associated costs to both individual and society, has led to scientific examination of the mechanisms which underpin dual-task gait performance. Typically, in experimental dual-task gait studies the participant walks over-ground on a straight walkway, or on a motorised treadmill, whilst gait performance is recorded (single-task gait). Participants are usually also required to perform the cognitive task when stationary and this is recorded as the single task performance for the cognitive task. Participants then perform the cognitive task whilst walking. Performance in both tasks (walking and cognitive) is recorded as the dual-task performance. Differences in task performance between the single and dual tasks, commonly referred to as the dual-task costs (Kelly et al., 2010; Yogev-Seligmann et al., 2010) are then suggested to reveal the dual-task effect, i.e. whether both tasks require access to the same cognitive resources (Yogev-Seligmann et al., 2008; Huang and Mercer, 2001).

2.1.5 Dual-Task Gait Costs

Unlike the AB and PRP dual-task models, dual-task gait allows analysis of task performance when two task are performed simultaneously. Performance in both walking and cognitive tasks during dual task gait are compared to performance under single-task conditions (Woollacott and Shumway-Cook, 2002). The most commonly reported dual-task effect on gait is a reduction in walking speed (Al-Yahya et al., 2011) suggesting that control of gait speed is partially reliant on cognitive resources (Beauchet et al., 2008). Because gait performance is usually typically impaired under dual-task conditions when compared to single task conditions, the effects of dual-task performance on gait are often referred to as dual-task costs (for e.g. Kelly et al., 2013). Whilst the prevalence of gait speed as an outcome measure in dual-task gait studies may in part be due to the relative simplicity of measuring it, changes in gait speed during dual-task gait have been suggested to clinically relevant and may be predictive of future falls in the elderly (Lundin-Olsson et al., 1997; Beauchet et al., 2008).

Another frequently reported consequence of dual-task gait is an increase in the stride to stride variability of temporal gait parameters (Al-Yahya et al., 2011). Gabell & Nayak (1984) suggested that stride time variability (STV) represents the automaticity of the stepping mechanism. Increased STV has been interpreted as a reduction in the automaticity, and increases in the cognitive control, of gait (Hausdorff, 2005). Thus, changes in STV are frequently used to assess changes in the cognitive control of gait (e.g. Gabell & Nayak 1984; Beauchet et al. 2005; Dubost et al. 2006; Frenkel-Toledo et al. 2005; Leitner et al. 2007; Bollens et al. 2014).

Increased (compared to healthy controls) STV has been reported in a number of cognitively impaired populations including Parkinson's disease, mild cognitive impairment and dementia (Frenkel-Toledo et al., 2005; Montero-Odasso et al., 2014; Allali et al., 2008) and these effects were often exacerbated during dual-task gait. However, decreased stride variability during dual-task gait has also been reported in dementia and ADHD patients (Leitner et al., 2007; IJmker and Lamoth, 2012). The cause of this discrepancy is not fully understood. The relationship between gait variability and gait stability is complex: both high and low stride variability are associated with gait instability (Beauchet et al., 2009a). Whilst high STV may represent pathological reductions in the automatic control of gait (Montero-Odasso et al., 2012), low variability may also represent pathological changes to gait control. A degree of gait variability is likely a required component of a flexible and healthy motor system because stride to stride variability allows the adaptation of gait in response to perturbations and facilitates balance during ambulation (Dingwell et al., 2010; Dingwell and Cusumano, 2010). Whilst the relationship between STV and functional gait performance is complex, it is nonetheless clear that dual-task gait reliably alters STV in cognitively impaired populations (Al-Yahya et al., 2011), indicating that STV is a sensitive marker of changes in the cognitive control of gait.

2.1.6 Factors Influencing Dual-Task Gait Performance

STV appears to be a sensitive measure of the magnitude of the cognitive control of gait in older adults and clinical populations. However, the effect of dual-task gait on STV in heathy adults is less clear. Although a number of researchers have reported that in healthy adults, dual-task gait does affect stride variability (Asai et al., 2013; Beauchet et al., 2005b; Springer et al., 2006; Yogev-Seligmann et al., 2008) a number of others have reported no changes (Yogev-Seligmann et al., 2010, 2008; Dubost et al., 2006; Beauchet et al., 2009b). The causes of this discrepancy are not fully understood. However, several factors may influence the dual-task cost on gait in healthy adults, including the constraints of both the walking and cognitive task, and prioritisation strategies.

2.6.1.1 Cognitive Task Type

The dual-task effect is mediated by the characteristics of the cognitive task. The cognitive load and the relative difficulty of the task (Huxhold et al., 2006), the stimulation modality (Liston et al., 2014) and response modality (Armieri et al., 2009) have all been reported to influence dual-task performance.

The nature of the cognitive task varies considerably across the dual-task gait literature. Al-Yahya and colleagues (2011) have categorised the cognitive tasks used in dual-task gait studies into five domains: reaction time tasks, discrimination tasks, verbal fluency tasks, working memory tasks and mental tracking tasks. Reaction time tasks require participants to respond to auditory or visual stimuli as quickly as possible. Discrimination tasks require participants to selectively attend to specific stimuli and respond accordingly (e.g. the Stroop task). Verbal fluency tasks require participants to spontaneously produce words within given search criteria. Working memory tasks require participants to hold and continuously update information in working memory (e.g. the N-back task). Mental tracking tasks require participants to both hold, update and manipulate information in working memory (e.g. serial subtraction tasks). Using these definitions, Al-Yahya et al., (2011) reported mental tracking and working memory tasks had a greater effect on gait than reaction time, verbal fluency or discrimination tasks. Al-Yahya et al., (2011) suggest that increased dual-task costs during performance of the working memory/mental tracking tasks is because of their increased demand on high level cortical structures (D'Esposito et al., 1995, 1999). However, this delineation based on cortical activation is problematic. Both working memory tasks and mental tracking tasks activate similar cortical networks (D'Esposito et al., 1995, 1999) yet there are contradictory reports of their effects on dual-task gait performance (Lövdén et al., 2008; Beauchet et al., 2005b). Instead of a cortical activation hypothesis, Beurskens & Bock (2012) instead suggest that it is differences in the cognitive processes taxed by each task which may underlie the opposing effects of each task on dual-task gait performance.

2.6.1.2 Walking task difficulty

The difficulty of the walking task may also influence dual-task gat performance. Kelly and colleagues (2010; 2013) increased the difficulty of the walking task by asking participants to walk naturally or with a narrow base. They reported that increasing walking difficulty changed healthy adults' task prioritisation during dual-task gait. Increasing walking difficulty may influence postural reserve, meaning greater attention must be paid to gait (Yogev- Seligmann et al., 2012). A number of studies have reported increases in STV when walking difficulty was manipulated by changing walking speed on a motorised treadmill. Walking at speeds below and above preferred walking speed increased STV, suggesting greater allocation of cognitive resources to the control of gait at these speeds (Jordan et al., 2007; Kang and Dingwell, 2008). Slow walking, in particular, appears to have a quadratic relationship with STV (Beauchet et al., 2009c). Old adults and clinical populations walk more slowly than healthy adults (Prince et al., 1997), but it is not clear whether this is a compensatory adjustment to maintain gait stability, or whether the slow walking may itself be more cognitively demanding, contributing to higher STV during dual-task gait in these populations (Beauchet et al., 2009c).

2.6.1.3 The Dual-Process Account of Dual-Task Gait Costs

Huxhold et al. (2006) proposed a dual-process model to explain the influence of cognitive task type and walking difficulty on the dual-task cost. They proposed that under conditions where the cognitive load imposed by either task is low (i.e. they are 'easy' to perform) then healthy adults allocate cognitive control away from the automatic task, gait, to cognitive task performance. This leads to an increase in automaticity, i.e. a reduction in STV. Conversely, when the cognitive load imposed by the tasks is high, (they are 'hard') then there is resource competition and dual-task costs are incurred in one or both of the tasks, increasing STV. Within this framework, reducing walking speed would increase dual-task costs because gait would require increased cognitive control, increasing STV, and this would lead to increased competition for cognitive resources. Similarly, one cognitive task may result in a reduction in STV (e.g. Lövdén et al. 2008) and another increase it (e.g. Beauchet et al. 2005) because of differences in the cognitive load (difficulty) imposed by each task.

2.6.1.4 Task Prioritisation Strategies

The dual-process account (Huxhold et al., 2006) presumes that healthy adults will always prioritise (i.e. allocate cognitive control toward) cognitive task performance, unless walking difficulty is increased and cognitive control must also be allocated to gait. However, prioritisation strategies may not be so rigid, and instead may be dependent on a number of individual and task dependent factors. Two prioritisation strategies have been identified: the posture first strategy, in which gait stability is prioritised over cognitive task performance, and posture second, where gait stability is sacrificed when walkers prioritise cognitive task performance (Shumway-Cook et al., 1997). Healthy adults have been suggested to prioritise gait stability whilst impaired and older adults were suggested to adopt a posture second strategy (Bloem et al., 2001). However, this dichotomous separation of task prioritization based on age fails to account for the reported discrepancies in the effect of dual-task gait on STV in healthy adults. Yogev- Seligmann and colleagues (2012) have instead proposed a model which accounts for the differences in dual-task performance between young, old and cognitively impaired older adults. Yogev- Seligmann et al. (2012) suggest that two factors influence whether an individual prioritises walking or cognitive task performance during dual-task gait: postural reserve and hazard estimation. Postural reserve refers to the walker’s ability to respond to perturbations and threats to stability during walking and is influenced by both muscle tone and flexibility, and cortical sensory-motor integration. Younger adults are presumed to have ample postural reserve. Conversely, age related declines in muscle tone and strength (Frontera et al., 2000; Goodpaster et al., 2006), and in proprioceptive and sensory apparatus (Goble et al., 2009) mean older adults have reduced postural reserve, and are thus required to pay more attention to gait. Hazard estimate refers to the cognitive status of the walker, specifically their ability assess internal and external threats to stability when walking which is related to the central executive functions. Inter and intra-individual variations in both postural reserve and hazard estimation influence task prioritisation during dual-task gait (Figure 2).

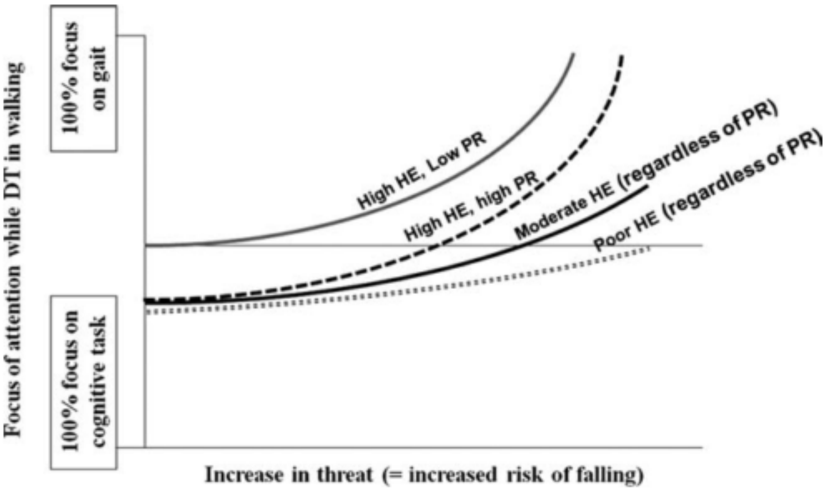

Figure 2. The interacting effect between postural reserve (PR) and hazard estimation (HE) on task prioritisation during dual-task gait. From Yogev- Seligmann et al. (2012).

Age, disease and developmental differences in musculature, sensory apparatus and cognitive capacity may account for individual variations in postural reserve and hazard estimation. Additionally, inter and intra-individual variations in both postural reserve and hazard perception may occur in response to changes in the environment, the nature of both the walking and cognitive task, and whether explicit instructions to prioritise on either tasks were given (Yogev- Seligmann et al., 2012). Individual allocation of cognitive control across tasks during dual-task walking is thus dependent on a number of factors: the nature of both tasks, their difficulty, and individual task prioritisation strategies, themselves influenced by the individual's physical and cognitive capacity.

2.1.7 Cognitive Capacity and Prefrontal Cortex

As detailed above, many factors appear to influence dual-task costs on gait, particularly on STV, a marker of cognitive control of gait. However, what is not clear currently is which neurophysiological mechanisms might underpin age related reductions in dual-task gait performance. One brain area repeatedly linked to the control of dual-task performance is prefrontal cortex, specifically lateral prefrontal cortex. Prefrontal cortex undergoes significant structural changes with age

(Dickstein et al., 2007) and these changes have been linked to alterations in gait performance in older adults (Rosano et al., 2012). Age related reductions in prefrontal cortex volume and function have long been linked to cognitive decline in older adults. The influential prefrontal cognitive aging hypothesis explicitly links reductions age related degeneration of prefrontal cortex to reductions in cognitive performance (MacPherson et al., 2002; West, 1996). Although this relationship has been challenged (Greenwood, 2000; Salthouse, 2011), changes to prefrontal cortex structure are linked to alterations to the cognitive control of gait and dual-task performance (Allali et al., 2010). Prefrontal cortex dependent cognitive functioning may thus be considered to influence dual-task gait performance.

In summary, using the dual-task paradigm a large and growing body of researchers have established a link between cognition and gait. Whilst there is increasing interest in the use of pharmacological and behavioural interventions to improve the cognitive control of gait, particularly dual-task gait (Montero-Odasso et al., 2012), it is necessary to first fully understand the mechanisms and structures involved in the control of dual-task gait performance. The next section will outline the evidence linking prefrontal cortex to dual-task performance and present relevant theories of prefrontal cortex function and how they may relate to the control of dual-task gait.

2.2 The Neural Control of Gait

The neural control of locomotion is achieved through the coordination of agonist and antagonist muscles groups by a range of spinal, brain stem and cortical structures and processes (Takakusaki, 2013). The following section will briefly outline the primary structures involved in this coordination, before presenting evidence for the involvement of prefrontal cortex in the control of gait.

2.2.1 Spinal and Brainstem Control of Gait

At the turn of the 20th century, Thomas Brown (1911;1914) reported that stimulating groups of spinal interneuronal networks produced rhythmic motion in the limbs of cats, even when feedback from sensory afferents and high-level brain centres was blocked. These mutually inhibiting interneuronal networks, which are referred to as central pattern generators (CPGs), are integral to the control of gait and are widely believed to be occur in all vertebrate mammals, including man (Duysens and Van de

Crommert, 1998). Stereotypic locomotor patterns and rhythms are generated by CPGs which both innervate and inhibit target motoneurons to produce phase dependent muscle activation (Guertin, 2009). Indirect evidence that humans possess spinal CPGs comes from studies examining stimulation of spinal structures in patients with spinal cord injury: Dimitrijevic et al. (1998) reported that stimulation of the L2 spinal segment produced a rhythmic stepping action in patients with complete spinal cord lesion and Calancie (2006) reported locomotor stepping patterns in patients with both complete and incomplete cervical spinal cord injury after spinal stimulation. Although direct stimulation of spinal centres suggested to contain CPGs can generate rhythmic gait patterns without supraspinal and sensory afferents (Grillner and Wallen, 1985; Duysens and Van de Crommert, 1998), muscle, cutaneous proprioceptive and sensory afferents also exert a profound controlling influence on CPG control of locomotion via feedback mechanisms which influence motoneuron drive during gait (Van de Crommert et al., 1998; Pearson et al., 1998; Aniss et al., 1992).

Brainstem and sub-cortical supraspinal structures influence CPG activity and locomotion. Although much of the current knowledge regarding the involvement of these structures has been derived from studies in decerebrate animals and non-human primates, recent studies using functional magnetic resonance imaging (fMRI) and single photon emission tomography (SPECT) have revealed activation in the brainstem and basal ganglia during human gait (Jahn et al., 2008; Fukuyama et al., 1997). Nuclei in the mesencephalon, referred to as the mesencephalic locomotor region (MLR) and others including the cerebellum and basal ganglia are all reported to exert descending influences on CPG activity (Yang and Gorassini, 2006). Decerebrate animals produce locomotor patterns if MLR is stimulated, and locomotion type (i.e. from walking to trotting to galloping) changes as stimulation intensity is increased (Douglas et al., 1993; Grillner, 1985). In vertebrates, MLR is suggested to initiate and receive afferent feedback from CPGs via the reticuospinal system, influencing locomotor responses to the environment (Grillner, 1985; Cohen et al., 1996). Some have suggested that MLR, specifically the pedunculopontine nucleus (PPN) is responsible for control of temporal gait patterns (Pahapill, 2000; Grabli et al., 2012). The PPN receives a number of direct connections from cortical motor areas and is considered one of the primary supraspinal centres involved in the control of gait (Benarroch, 2013). The basal ganglia also mediate CPG activity, specifically muscle tone and locomotor pattern generation, via inhibitory and excitatory modulation of the MLR\PPN, controlling and initiating CPG activity (Takakusaki et al., 2004; Takakusaki, 2013). The cerebellum has been suggested to regulate both voluntary and automatic movements (Morton and Bastian, 2004). The cerebellum exerts influence on both cortical and brainstem structures and lesion evidence suggests that cerebellar processes may modulate the output of CPGs (Morton and Bastian, 2004, 2007; Takakusaki, 2013).

2.2.2 Cortical Control of Gait

Historic descriptions of the neural control of gait control predominantly focussed on the spinal and lower brain regions, which account for the largely automatic processing of gait patterns (Shik and Orlovsky, 1976). However, gait can be considered a goal directed behaviour, and as such requires input from high-level volitional and cognitive processes which originate from higher cortical centres (Takakusaki, 2013). Accordingly, Takakusaki (2013) has proposed a model for the neural control of locomotion in vertebrates which integrates cortical, brainstem and spinal inputs (Figure 3).

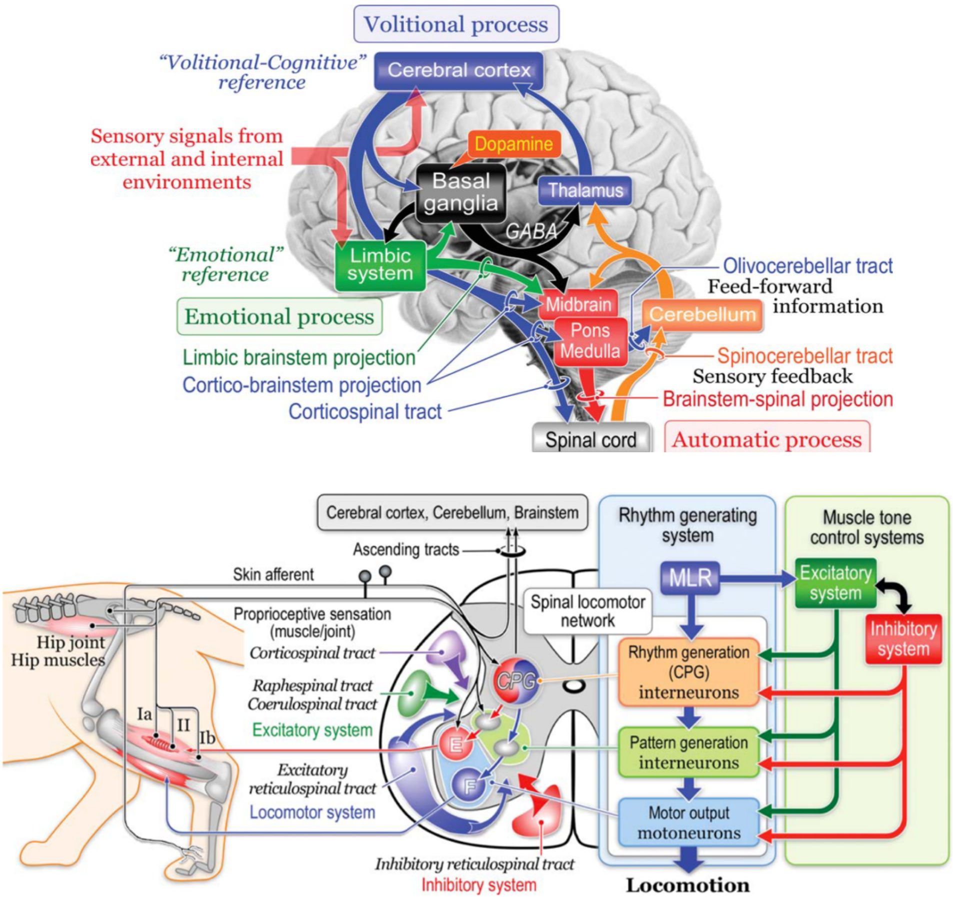

Figure 3. Neural control of gait. Recent models of the control of gait highlight the influence of cortical regions in the volitional control of gait. Adapted from Takakusaki (2013).

In non-human animals, primary motor cortex is suggested to be involved in the initiation and cessation of CPG activity, altering stepping patterns in response to environmental perturbations (Armstrong, 1988; Drew, 1993). In humans, primary motor cortex projects directly onto motoneurons via the cortico-motoneuronal pathway (Lemon, 2008) and projects directly to the MLR\PPN (Monakow et al., 1979). Capaday et al., (1999) reported similar motor cortex activation during both walking and seated dorsiflexion, which they suggested indicated that motor cortex was involved in the control of ongoing gait. Using sub-threshold Transcranial Magnetic Stimulation (TMS) to activate inhibitory intracortical circuits within motor cortex, Petersen et al., (2001) suppressed lower limb muscle activity during walking, which they suggested indicates that motor cortex and the corticospinal pathway are directly involved in muscle activation during ongoing gait.

Supplementary motor area, which projects to both the basal ganglia and directly to motoneurons through the corticospinal pathway, is suggested to be involved in internally triggered\self-initiated movement (Hiroshi, 2012). Supplementary motor area may also be involved in the initiation of gait via activation the lower locomotor centres, especially in response to environmental cues, and in feed forward adjustments to posture and balance during gait initiation (Fukuyama et al., 1997; Takakusaki, 2013; Nachev et al., 2008; Suzuki et al., 2008). Pre-motor cortex has been linked to the sensory guided adjustments of motor performance, particularly those guided by visual cues. In mammals, posterior parietal cortex and vestibular cortex are suggested to integrate visual and vestibular information, from which pre-motor cortex creates a motor program which assimilates information about the environment and the body's place within it (Takakusaki, 2013). In monkeys, pre-motor cortex lesions prevent monkeys performing and re-learning previously learnt visual cue tasks (Halsband and Passingham, 1982). In humans, Schluter et al. (1998) used TMS to temporarily disrupt pre-motor cortex and reported decreased performance in a visually cued reaction time tasks, supporting the suggestion that the pre-motor cortex also plays a role in the assimilation of visual cues in human motor performance. Suzuki et al. (2004) used functional near infrared spectroscopy (fNIRS) to monitor cortical activation during gait and reported increased pre-motor cortex activation when participants' adjusted gait to match changing treadmill speeds, indicating an involvement of the pre-motor cortex in the adaptation of motor output in response environmental perturbations.

2.2.3 Prefrontal Cortex and Gait

Recent models of the control of locomotion now highlight the involvement of the frontal cortex in the control of gait (see Figure 3, above). Evidence from both lesion and imaging studies indicate that prefrontal cortex is involved in gait control. In their seminal paper, Nutt and colleagues identified a range of gait disorders from their clinic which were linked to frontal pathology, which they termed higher level gait disorders (HLGD, Nutt et al. 1993). Recently, Nutt and colleagues have refined their classification of HLGD into two subtypes: frontal and posterior HLGD (Nutt, 2013). Age related changes in prefrontal volume (Rosano et al., 2012), and white matter integrity (de Laat et al., 2011) have been linked to frontal HLGD. In healthy adults, Malouin et al (2003) reported increased prefrontal cortex activation, using positron emission topography, during a walking imagery task. During real gait, a number of researchers using fNIRS have shown prefrontal cortex to be activated during both gait preparation (Suzuki et al., 2008) and during adaptation to both changing gait speeds and challenging gait conditions (Suzuki et al., 2004; Koenraadt et al., 2014). Koenraadual and colleagues (2014) reported that prefrontal cortex activation increases during "precision stepping" where the walker is required to pay attention to their foot placement. They suggested that prefrontal cortex is involved in the allocation of attention during gait. Although prefrontal cortex does not project directly to corticospinal or brainstem areas, dorsolateral prefrontal cortex projects to the premotor cortex, as well as parietal, cingulate and insula cortices (Hoshi, (2006), Figure 4) and it is through these pathways that prefrontal cortex may exert influence on neural locomotive structures.

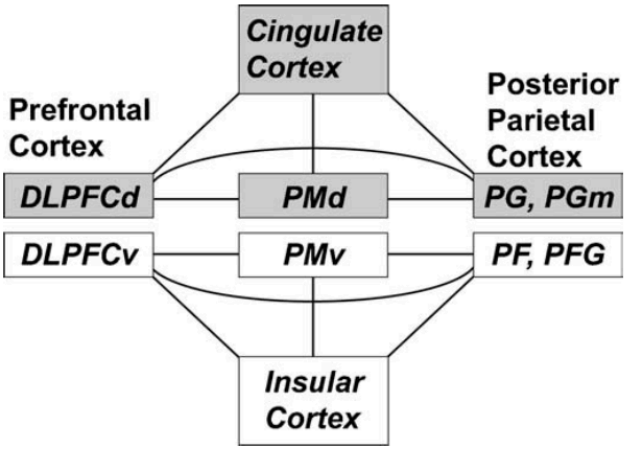

Figure 4. Anatomical connection of the lateral prefrontal cortex. Adapted from Hoshi, (2006)

2.2.4 Prefrontal Cortex and Dual-Task Gait

There is considerable evidence that prefrontal cortex is involved in the control of dual-task gait. Lesion evidence has long linked prefrontal cortex to dual-task performance. Baddeley et al. (1997) examined a mixed group of frontal lesion patients, which they separated into two groups, a dysexecutive group, who had undergone significant cognitive and behavioural changes, and the non-dysexecutive group, who had not. They reported that the dysexecutive group performed significantly worse in dual working memory and visual tracking tasks, indicating prefrontal cortex involvement in dual-task performance. These results have been confirmed in fMRI studies which have shown increased prefrontal cortex activation during (non-gait) dual-task performance (Collette et al., 2005; Dreher and Grafman, 2003; Szameitat et al., 2002).

Perhaps the most compelling evidence linking prefrontal cortex to dual-task gait performance comes from work using fNIRS during dual-task walking. Holtzer et al. (2011) first reported increased prefrontal cortex activation during dual-task gait. Comparing prefrontal cortex activation during normal and dual-task walking, Holtzer et al. (2011) reported increased prefrontal cortex activation in both old and young adults. However, younger adults displayed significantly higher activation than older adults. This result was replicated by other groups in cohorts of healthy young, old and cognitively impaired adults (Doi et al., 2013; Meester et al., 2014; Atsumori, 2010; Lu et al., 2015). Somewhat in contrast to these findings, Beurskens et al. (2014) reported decreased prefrontal cortex activation in older adults and no changes in prefrontal cortex activation in younger adults during dual-task gait. However, this discrepancy maybe due to differences in the relative difficulty of the cognitive tasks used. Support for this suggestion can be found in the study by Mirelman et al. (2014) who examined the influence of task difficulty on prefrontal cortex activation and the relationship between prefrontal cortex activation and STV during dual-task gait. In this study, prefrontal cortex activation was compared during quiet standing, standing whilst counting backwards in sevens, walking whilst counting forwards in ones and walking whilst counting backwards in sevens. Mirelman et al., (2014, Figure 5A) reported increased prefrontal cortex activation during both dual-task conditions, and a significantly higher increase in prefrontal cortex activation in the more complex dual-task condition (counting backwards in sevens) compared to the simpler condition (counting forwards in ones).

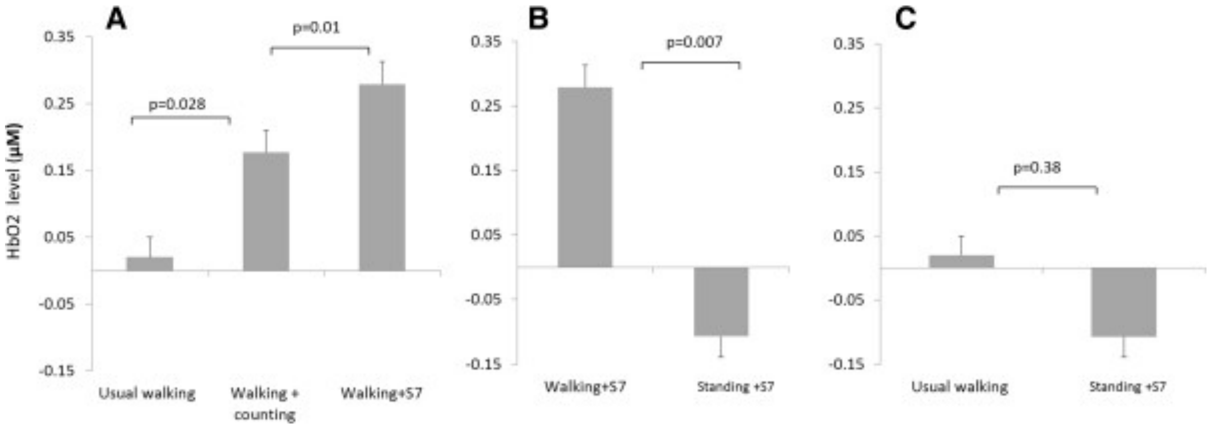

Figure 5. Prefrontal cortex activation, assessed by HBO_2 levels (µM), during dual-task gait. Prefrontal cortex activation was highest during the more complicated walking and serial subtraction conditions, compared to all other conditions (A) and (B). Dual-task standing decreased prefrontal cortex activation compared to normal walking (C). From Mirelman et al. (2014).

Interestingly, standing when performing a dual-task decreased prefrontal cortex activation compared to normal walking, indicating that it is only the simultaneous performance of both motor task (standing and walking) and counting backwards in sevens that activated prefrontal cortex. Mirelman et al. (2014) also reported a negative correlation between prefrontal cortex activation and number of subtractions (r=-0.71, p=0.011): prefrontal cortex activation was lower in those who found the cognitive task harder (i.e. made fewer subtractions). This relationship suggests that prefrontal cortex activation during dual-task gait is dependent on the relative difficulty of the combined task.

In summary, gait is controlled through the integration of a myriad of spinal and supraspinal processes and neural structures. Both lesion and imaging studies have revealed that prefrontal cortex is activated during gait. Some have suggested that the role of prefrontal cortex during gait is to allocate attention toward gait performance. The link between prefrontal cortex activation and dual-task gait performance indicates that prefrontal cortex may be part of central resource controlling dual-task gait performance. Recent imaging evidence suggests a complicated relationship between prefrontal cortex activation and dual-task gait demands, in which prefrontal cortex activation may be determined by individual task performance behaviour. Currently however, the role of prefrontal cortex in the cognitive control of dual-task gait remains unclear. In order to provide a theoretical framework against which the role of prefrontal cortex in the cognitive control of dual-task gait can be examined, the following section will present prominent theories of prefrontal cortex function and dual-task performance.

2.3 Prefrontal Cortex and Cognitive Control

Prefrontal cortex has been linked to a bewildering number of cognitive functions (Fuster, 2013) which are the basis of many neurobiological models of cognition (e.g. Fuster 2001; Passingham & Wise 2012; D'Esposito 2007). For brevity, this thesis will outline the most prominent theories of cognitive control by prefrontal cortex which are relevant to dual-task performance: the central executive and executive functions theory (Baddeley, 2003; Baddeley and Hitch, 1994; Miyake et al., 2000) and the guided activation\neural bias theories of cognitive control (Miller, 2000; Miller and Cohen, 2001; Cohen et al., 2004). Both frameworks address the role of prefrontal cortex in the cognitive control of behaviour, and both are used to interpret causal relationships between prefrontal cortex and dual-task performance (e.g. Johnson et al., 2007).

2.3.1 Working Memory and Executive Control

Working memory has been defined as a "limited capacity system, which temporarily maintains and stores information, supports human thought processes by providing an interface between perception, long-term memory and action" (Baddeley, 2003, p 829). Baddeley's working memory models identified four main components, a central executive and three limited capacity slaved components. The first two are the phonological loop and the visual-spatial sketchpad. Both hold resource specific (phonological and visual) information in accordance with multiple resource models of dual-task performance (Wickens, 2002). A third slaved component, the episodic buffer, acts as a temporary store, involved in the transfer of items to and from long term memory, and with the other slaved components (Baddeley, 2000).

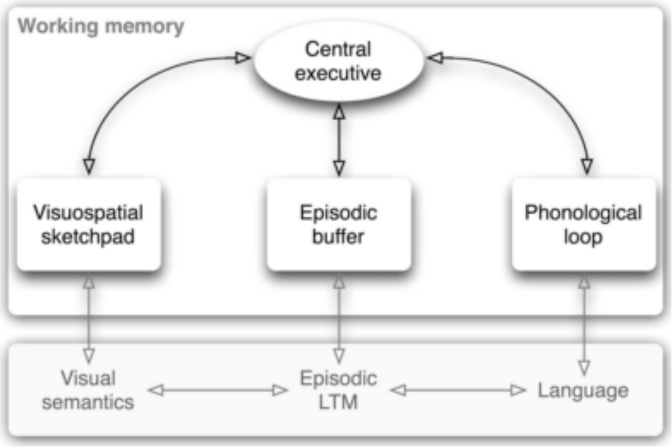

Figure 6. The working memory model, from Repovs and Baddeley (2006).

At the apex of the working memory hierarchy is a limited capacity central executive, which allocates cognitive resources based on task demands (Figure 6). Repovs & Baddeley (2006) suggest that the central executive is involved in the allocation and division of attention/cognitive resources to one or many tasks. The central executive is thus conceived as a supervisory cognitive control system which exerts top down control over the slaved working memory sub systems, the phonological loop, visuospatial sketchpad and episodic buffer. As such, the central executive can be considered analogous with the concept of the supervisory attention system proposed by Norman and Shalice (1986) which was suggested to exert cognitive control in situations in which the automatic or habitual response may be inappropriate. Baddeley (1996) postulated that the central executive exerted control through four executive processes: the ability to transfer the contents of the limited capacity working memory system to long term memory and the allocation, switching and division of attention.

An influential paper by Miyake et al. (2000) identified three core executive functions which are closely linked to Baddeley’s (1996) executive processes. These were the inhibition function, which allows one to supress dominant but task irrelevant responses, the shifting function which allows one to shift attention and activate task-rules between different tasks, and the updating function in which the contents of working memory are monitored and manipulated. Recent accounts of the executive functions define them as “family of top-down mental processes needed when you have to concentrate and pay attention, when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible” (Diamond

2014, p135). They are thus synonymous with both the supervisory control system (Norman and Shalice, 1986), and the central executive (Baddeley, 1996). Diamond (2014) identifies three core executive functions which broadly mirror those of Miyake et al. (2000): inhibition, flexibility (a shifting function) and working memory, which shares many properties with the updating function. Dual-task performance has been suggested to arise from interactions between core executive functions (Logan and Gordon, 2001). Others (e.g. Baddeley (1996), Logie et al. (2004)) add a fourth executive function: a specific dual-task function, which is an individuals' ability to perform two tasks simultaneously. Aside from these three often identified 'core' executive functions, there are a number of other defined executive functions which include volition, planning, purposeful action and effective performance amongst others (see Lezak, 2004; Jurado and Rosselli, 2007 for a review).

Since its conception, the central executive and the executive functions have been linked to prefrontal cortex. A number of studies reported that patients with frontal lobe lesion display reduced performance in tasks which test executive function capacity (Andrés, 2003). The advent of neuroimaging techniques revealed increased prefrontal activation during executive function tasks (Wager and Smith, 2003). Szameitat et al. (2002) reported increased prefrontal cortex activity during dual-task performance, itself influenced by the addition of a task switching component, which the authors suggested linked prefrontal cortex to executive dual-task control. However, the 'seating' of the central executive and executive functions, including dual-task functions, in prefrontal cortex has been criticised by some. Some lesion studies reported no decrements in dual-task performance in patients with frontal lesions (Frisk and Milner, 1990; Baddeley et al., 1997; Andrés and Linden, 2002) and other neuroimaging studies have shown increases in various other cortical areas during working memory/central executive processing (Wager and Smith, 2003). Andrés (2003) instead suggested that central executive processing was distributed across a number of brain regions, a central executive network. This distributed network is suggested to be involved in top down control of cognitive processes, including the simultaneous performance of two cognitively demanding tasks (Eriksson et al., 2015).

2.3.2 Executive Control and Dual-Task Gait

The executive function model of cognitive control has been hugely influential in the study of dual-task gait performance (Yogev-Seligmann et al., 2008). Sheridan et al. (2003) reported that Alzheimer's disease patents STV increased by 36% during dual-task walking, and this increase was correlated with performance in the Mini Mental State Examination test of executive function (r=0.47, p=0.011). Springer et al. (2006) examined the relationship between executive function and fall-risk in order adults. Using the Stroop test of inhibition, they reported a correlation between executive function and swing time variability in old adults (r= 0.63, p=0.001). Beauchet et al. (2012) examined the relationship between the three core executive functions, updating, inhibition, and shifting, with STV in healthy adults' single task walking. Beauchet et al. (2012) reported that high STV was related to the updating function, assessed using the digit span memory test (Odds Ratio=0.78, p=0.020) and suggested that the control of gait is related to this specific executive function only.

Although there is a great deal of theoretical and empirical evidence linking prefrontal cortex to executive control and the central executive, theories of executive control often give little indication as to *how* prefrontal cortex exerts cognitive control over tasks. Indeed, a major criticism of the central executive theories is that, because they place prefrontal cortex and its networks as orchestrators of behaviour, they require a homunculus or executive controller to decide when to inhibit, update or to switch (Jurado and Rosselli, 2007; Hazy et al., 2007; Verbruggen et al., 2014). In order to address these issues, several neuropsychological theories have been proposed which describe how prefrontal cortex exerts executive/cognitive control through neural bias of gonging neural processing.

2.3.3 Prefrontal Cortex and Neural Bias: The Guided Activation Theory

Perhaps the most influential model for how prefrontal cortex exerts cognitive control is the guided activation theory (Miller and Cohen, 2001; Cohen et al., 2004). The guided activation theory describes how cognitive goals are used to control behaviour in situations where more automatic responses may be inappropriate. Guided activation can be considered an extension of the biased competition theory of Desimone & Duncan (1995) in which processes in the brain are suggested to compete for shared resources. The biased competition theory postulates that behaviour is determined by the competition between mutually inhibitive task dependent pathways. The more active pathway wins the competition, and top down allocation of attention increases the pathway activation (Desimone & Duncan 1995). Extending this work, the guided activation theory posits that prefrontal cortex maintains representations of task relevant goals and the means to achieve them (Miller and Cohen, 2001). Attention is defined as the influence of these representations on the processing of other representations (Cohen et al., 2004). Rather than actively orchestrate top down control of cognition, under the guided activation theory prefrontal cortex instead biases ongoing task-relevant neural processing, ensuring the correct mapping between sensory inputs, internal states and motor outputs. Importantly, under the guided activation theory prefrontal cortex is modulatory and not transmissive, executive control instead involves the active maintenance of task relevant goals and rules (Miller and Cohen, 2001). Prefrontal cortex representations are created through Hebbian mechanisms (Hebb, 2005) mediated by dopaminergic reward pathways during associative learning.

Braver and colleagues (Botvinick et al., 2001; Braver, 2012) also highlight the role of prefrontal cortex in the goal-related bias of ongoing neural processing. Extending the guided activation theory, the dual-mode theory of cognitive control posits that cognitive control is exerted through two distinct operations: a proactive mode, analogous with guided activation, where prefrontal cortex exerts bias over ongoing neural processes based on goal-related representations, and a reactive mode, where cognitive control is utilised in an ad-hoc manner (Braver, 2012). Both modes activate prefrontal cortex; the proactive mode in a sustained manner and the reactive mode in transient manner, mediated by areas known to be involved with conflict resolution such as the anterior cingulate cortex

Prefrontal cortex receives information from a large number of sensory, motor and mid brain structures (Figure 7). Miller and Cohen (2001) identify four separate areas of prefrontal cortex: the orbital and medial areas, the dorsolateral area, the ventrolateral areas and the mid dorsal area. Each has their own set of connections to motor, sensory and mid and deep brain structures.

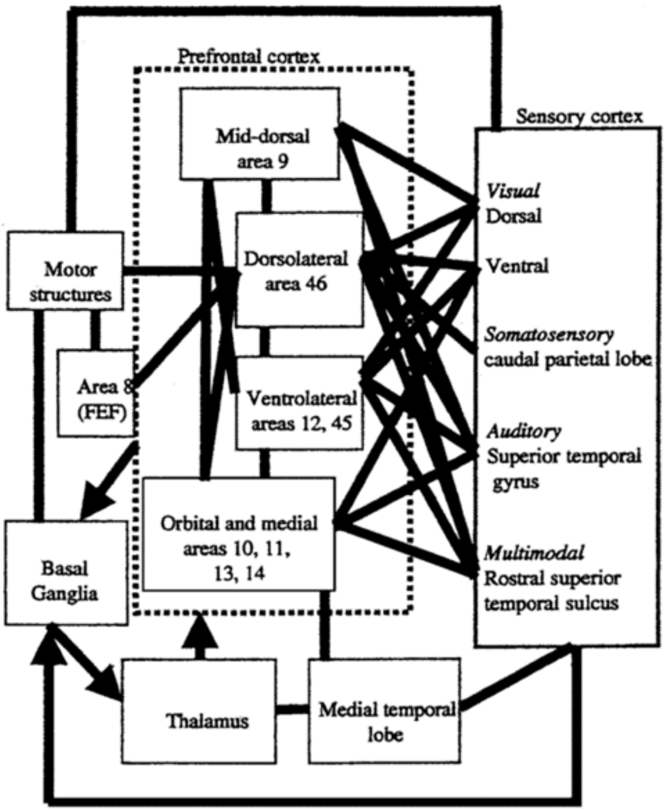

Figure 7. The connections of prefrontal cortex - Schematic showing the afferent and efferent connection between prefrontal cortex and sensory, motor, sensory and deep brain structures. From Miller and Cohen (2001)

Prefrontal cortex is amongst the most globally connected structures within the brain (Cole and Schneider, 2007; Cole et al., 2010). Miller and Cohen (2001) suggest that it is through these afferent and efferent connections that prefrontal cortex exerts top-down control through the integration and biasing of competing networks. That is, based on task relevant goals and the integration of sensory and internal state information, prefrontal cortex modulates ongoing neural pathways, guiding activity along task relevant neural pathways in posterior and sub-cortical brain areas, and inhibiting task irrelevant processes, resulting in task appropriate behaviour (Miller and Cohen, 2001).

The guided activation model is analogous with the concept of automatic vs controlled processing (Shiffrin and Schneider, 1976). Well practiced tasks require less bias from prefrontal cortex because their repetition has induced plastic changes which result in efficient neural activation in response to the task demands. In contrast, novel or less well learned tasks would require greater activation from prefrontal cortex to bias neural pathways based on task goals (Miller 2000). Miller and Cohen (2001) provide a vivid example of the effects of guided activation on behaviour: an American citizen upon visiting Britain for the first time would be required to exert cognitive control when crossing the road. Their automatic behaviour would be to look to the left to check for oncoming traffic. However, whilst in Britain, visual cues would activate internal representations within prefrontal cortex, which would bias excitatory signals that would cause them to look to the right. Repeated activation of these pathways and subsequent dopaminergic reward feedback loops, would increase prefrontal cortex connections which underlie this behaviour, meaning that the behaviour, looking right, becomes more automatic and requires less top down control the longer the American is in Britain.

In recent years, the neural structures involved in cognitive control have been expanded to include distributed cognitive control networks. Cole & Schneider (2007) examined activation correlations between brain areas during cognitive control and identified a cognitive control neural network, which included prefrontal cortex, anterior cingulate and insular cortices, as well as premotor and parietal areas. Using resting state fMRI, Cole and colleagues (2010; 2013) subsequently provided evidence that this fronto-parietal control network (FPN) was densely connected to other neural networks involved in cognitive control. Cole et al. (2013) suggest that the FPN was comprised of densely interconnected neural hubs, including prefrontal cortex, which altered connectivity patterns to other cognitive control networks based on task demands. It is through these flexible interconnections that FPN is suggested to mediate behaviour. Unsurprisingly, this cognitive control network appears to be involved in executive control. Niendam et al. (2012) provided meta-analytic evidence of FPN activation during executive function tests from over 190 fMRI studies. Thus, recent evidence confirms the prominence of prefrontal cortex in cognitive control, but instead places it in a distributed neural network involved in cognitive control the FPM. In their “flexible hub” theory, an extension of the guided activation theory, Cole and colleagues suggest that the FPN helps to co-ordinate cognitive control through alterations in connectivity with other cognitive control networks.

2.3.4 The Guided Activation Theory, Executive Control and Dual-Task Gait Performance

Under the guided activation theory, the role of prefrontal cortex/FPN, during dual-task performance would be to bias task relevant, and inhibit task-irrelevant, information and behaviour. These functions might be considered analogous to the executive functions, where active maintenance, inhibition, updating and conflict resolution of task goals and rules are performed by prefrontal cortex (Miller and Cohen, 2001). Under the guided activation theory, during dual-task performance both tasks would have competing prefrontal cortex representations, and this competition is the basis for the dual-task effect (Cohen et al., 2004; Botvinick et al., 2001). Importantly the strength of the representations would determine the size of this effect. For example, an "automatic" task would require less cognitive control, and so simultaneous performance of an automatic and a cognitively demanding task may not lead to decrements in task performances. In contrast, performance of two controlled tasks, with competing prefrontal cortex representations, may result in reduced task performance (Cohen et al., 2004).

This distinction is the basis of the dual-process account of dual-task performance (Huxhold et al., 2006) which suggests that during performance of low difficulty tasks, which require less cognitive control, performance in a motor task is unaffected or even improved as both tasks are performed "automatically" i.e. with minimal cognitive control. However, performance of more difficult tasks requires greater top-down cognitive control, leading conflict between prefrontal cortex representations for both tasks and dual-task decrements (Cohen et al., 2004; Botvinick et al., 2001). Lövdén and colleagues examined this dual-process account of dual-task performance by manipulating the effect of working memory task difficulty on gait variability during dual-task walking (Lövdén et al., 2008; Verrel et al., 2009; Schaefer et al., 2010). They reported that increasing task difficulty in older adults and children resulted in increased gait variability, indicating increased cognitive control (Verrel et al., 2009; Schaefer et al., 2010). In healthy adults however, they reported reduced variability across all difficulties (see Figure 8) which they suggested indicated reduced cognitive control of gait (Lövdén et al., 2008; Schaefer et al., 2010).

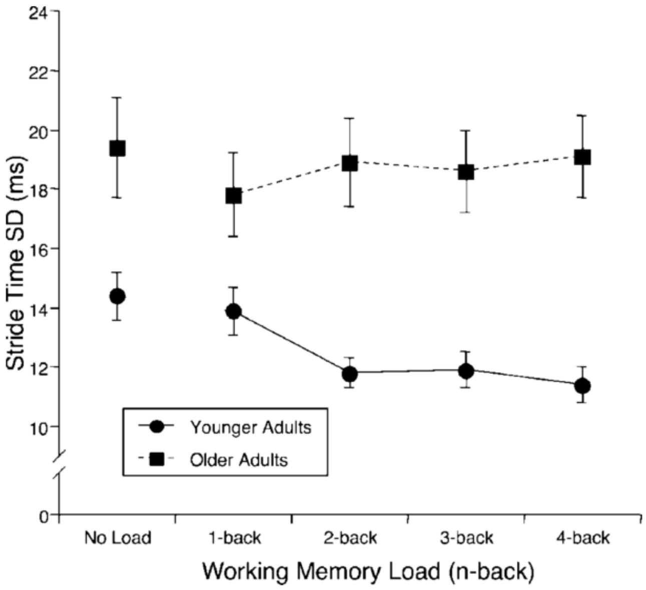

Figure 8. Changes in stride time variability (standard deviation of stride time) during single task (walking only) and dual-task walking in young and old adults. Cognitive task difficulty was manipulated by increasing the demands on working memory during an N-back test. From Lövdén et al., (2008).

Under the guided activation theory, prefrontal cortex/FPN would bias the control networks involved in task processing for both tasks during dual-task performance, based on the strength of the task relevant goal representations held in prefrontal cortex (Miller and Cohen, 2001; Cohen et al., 2004). Speculatively, one might assume that the strength of these representations and their bias over the direction of attention could alter implicit task prioritisation behaviour during dual-task gait. Limited support for this suggestion can be found in the evidence examining the effect of age on task prioritisation during dual-task performance. Prefrontal cortex undergoes significant morphological, neuro-chemical and electrophysiological changes in old age (Dickstein et al., 2007). Hobert et al. (2011) reported that performance in the trial making test of executive function, which activates prefrontal cortex (Zakzanis et al., 2005), was related to task prioritization during older adult's dual task gait.

2.3.5 Summary and Limitations

The central executive and guided activation frameworks have been influential in the examination of dual-task performance and cognitive control. The central executive model posits that core executive functions underlie much of the behaviour in tasks which require substantial top-down cognitive control, that is, are not performed automatically. The guided activation theory and its recent extensions provide a neuropsychological model of how this is achieved. Under this model, prefrontal cortex lies within a cognitive control network densely interconnected with other neural networks. This network provides cognitive control by biasing and inhibiting ongoing neural processing based on task relevant goals and rules contained within prefrontal cortex. Under this model, dual-task effects could occur when two tasks both requiring top down control activate competing prefrontal cortex representations. The guided activation theory thus provides a useful framework against which the role of prefrontal cortex in the control of dual task gait can be analysed.

Whilst there is a growing body of imaging research linking prefrontal cortex activation with dual-task gait performance, as yet the role of prefrontal cortex is unclear. One of the frequent criticisms of imaging evidence is that, unlike lesion studies, it does not provide causal evidence for the involvement of a structure or network in task performance (Passingham and Wise, 2012). Although technical advances using fMRI help to address this issue (Passingham et al., 2013; Poldrack and Farah, 2015), most imaging dual-task gait studies employ fNIRS, due to its portability (Holtzer et al., 2014). Lesion evidence is also not without issues; whilst it can provide causal evidence that a brain region or network is involved in task performance, results can often be contradictory, with some lesion patients able to perform as well as controls in tasks assumed to require the lesioned brain area (Andrés and Linden, 2002). Compensatory chronic plastic changes in response to insult, insult to multiple structures or general intrinsic redundancy in brain function limit the interpretation of clinical lesion studies (Rorden and Karnath, 2004). There is therefore a requirement to utilise novel techniques, such as transcranial brain stimulation, in order to examine the relationship between brain areas and networks to behavioural outcomes (Pascual-Leone et al., 2000; Filmer et al., 2014).

2.4 Using Transcranial Direct Current Stimulation to Examine Brain Function

It is possible to use non-invasive brain stimulation techniques to modulate cortical activity and examine resultant changes in performance (Filmer et al., 2014). Transcranial direct current stimulation (tDCS) is one such technique which has been used to examine the role of prefrontal cortex on dual-task performance. The following section will present a brief history of tDCS, proposed mechanisms by which tDCS elicits effects and the results of tDCS studies examining the role of prefrontal cortex in dual-task gait.

2.4.1 Historical use of tDCS

Early uses of electricity to alter brain activity and examine brain function can be traced back to ancient times: Scrobonius Largus, physician to the Roman emperor Claudius, was reported to have used electric fish to bring about a temporary stupor (Kellaway, 1946). Electrical stimulation was only sporadically examined throughout the intervening years, as the techniques could often be painful (Stagg and Nitsche, 2011). Modern interest in the effects of electrical currents on brain function was reignited after the invention of TMS by Barker and colleagues (1985). By examining the properties of the motor potential evoked by TMS (motor evoked potential, MEP), researchers were now able to quantify the excitability of motor cortex and corticospinal tract. Excitability changes following weak electrical stimulation (for e.g. tDCS), which had been difficult to quantify before TMS, now became possible.

The first modern application tDCS used TMS to examine the effects of passing low levels of electric current transcranially onto motor cortex. In their pioneering studies, Nitsche and Paulus (2000, 2001) used a current intensity of 1 mA and examined the effect of anodal (where the anode is placed over motor cortex) and cathodal (where the cathode is placed over motor cortex) stimulation on corticospinal excitability. Nitsche and Paulus (2000) reported a polarity dependent effect of electrical stimulation: anodal electrical stimulation increased MEP amplitude size, which indicates increased corticospinal excitability. Conversely, cathodal stimulation decreased MEP amplitude\corticospinal excitability (Figure 9).

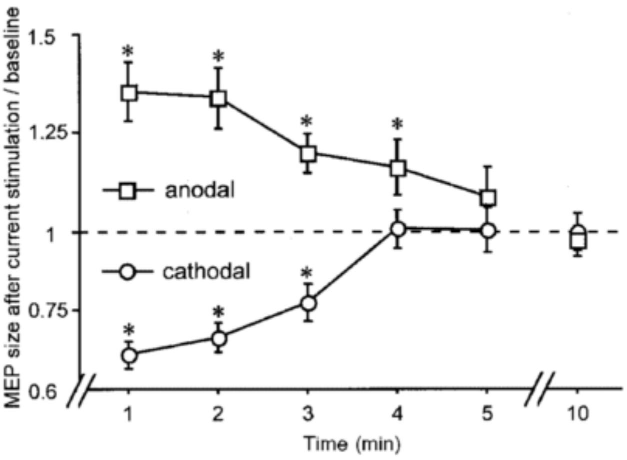

Figure 9. Polarity dependent changes in motor cortex excitability following 1 mA tDCS. From Nitsche & Paulus (2000).

Polarity dependent shifts in motor cortex excitability following tDCS were subsequently replicated by a number of groups (Jacobson et al., 2012). Examining task performance before and after transient changes to neural activity following TMS was already an established method to examine brain and behaviour relationships (Walsh and Cowey, 2000). tDCS was subsequently employed as a both a method to examine the contribution of brain structures and networks to task performance (Filmer et al., 2014) and as a possible treatment to improve cognitive and motor functions (Schulz et al., 2012).

2.4.2 Physiological Effects of Acute tDCS

During tDCS low levels of current are delivered via rubber electrodes, covered in saline soaked sponges, through the skull to cortical areas underlying the stimulation site (Nitsche et al., 2008). There are two electrodes: an active electrode and a reference electrode. Whether the electrode is active or reference depends on it positioning: the active electrode is placed over the targeted area (e.g. motor cortex) and the reference electrode over a remote place on the skull, or on the body (Nitsche et al., 2008). In the tDCS circuit one electrode is referred to as the anode (positively charged) and one as the cathode (negatively charged). Current flows from anode to cathode. The active electrode can either be the anode or the cathode. If the active electrode is the anode, the stimulation is referred to as anodal tDCS, if it is the cathode, as cathodal tDCS (Nitsche et al., 2008). Because current flows through the reference electrode, it is not inert but is actively involved in the injection of current through the brain to the targeted cortical area (Miranda et al., 2006).

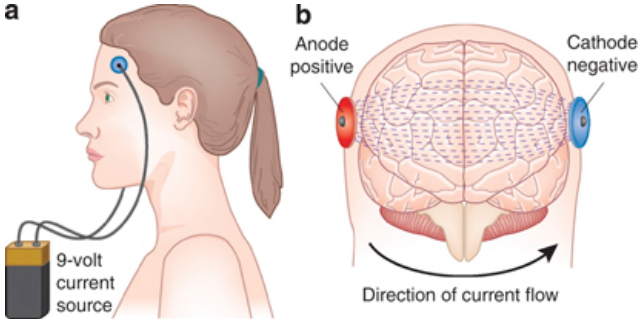

Figure 10. A typical tDCS montage, showing the flow of current from anode to cathode. From George and Aston-Jones, (2010).

Initial models of tDCS effects were based primarily on the findings of Nitsche and Paulus (2000, 2001) and their subsequent replications. Anodal tDCS was reported to increase, and cathodal tDCS decrease, neuronal excitability (Nitsche et al., 2008). In animal models of electrical brain stimulation, anodal stimulation depolarises and cathodal stimulation hyperpolarises neuronal cell membranes (Bindman et al., 1964). During stimulation, tDCS appears to modulate neuronal cell membrane potential in the same manner. tDCS has been reported to induce polarity dependent shifts in corticospinal excitability (Nitsche and Paulus, 2000, 2001). Application of sodium channel antagonists attenuates acute tDCS induced excitability changes, suggesting that tDCS alters neuronal excitability through changes to sodium influx (Nitsche et al. 2003; Liebetanz et al. 2002). Nitsche et al. (2005) examined the effects of acute tDCS (4 s of stimulation) the MEP recruitment curve, which reflects the amplitude of the TMS evoked MEP in relation to the applied pulse strength, and on intracortical facilitation and inhibition. They reported a polarity dependent shift in the MEP recruitment curve where anodal tDCS increased the slope of the curve (reflecting increased excitability) whilst cathodal tDCS diminished it, supporting the suggestion that during stimulation tDCS acts directly on cell membrane excitability. There was no effect of anodal tDCS on intracortical facilitation or inhibition, suggesting that during stimulation tDCS does not influence synaptic transmission.

2.4.3 Physiological Effects of Long-Term tDCS

If tDCS is applied for five minutes or over (long-term tDCS), polarity dependent shifts in excitability can last up to 1 hour. The time course of long-term effects is dependent on stimulation duration. Stimulation of five minutes can lead to changes in cortical excitability that last up to 15 minutes after stimulation cessation, whilst stimulation for over 13 minutes can last up to 60 minutes (Nitsche and Paulus, (2001), Figure 11). These effects mirror those seen in animals, where direct anodal electrical cortical stimulation of over five minutes led to long term increases in peak to peak amplitude of evoked potentials (Bindman et al., 1964).

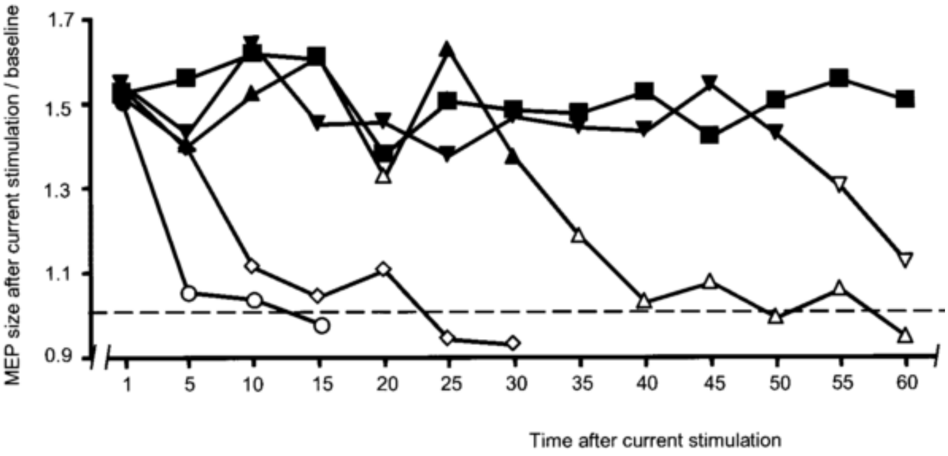

Figure 11. Time course of the effects of anodal motor cortex tDCS (1 mA) on corticospinal excitability. Symbols indicate tDCS duration: circles = 5 minutes, diamonds = 7 minutes, upward-pointing triangles = 9 minutes, downward-pointing triangles = 11 minutes, squares = 13 minutes. Filled symbols represent significant changes in MEP amplitude compared to baseline. From Nitsche & Paulus (2001).

Although the mechanisms underpinning the sustained changes in excitability are still unclear, it is speculated that the long-term effects are due to changes in both membrane potential and synaptic activity. As with acute effects of tDCS, long term changes to cortical excitability following stimulation are abolished with calcium and sodium channel blockers, implicating changes in cell membrane excitability in the long term effects of tDCS (Nitsche et al., 2003b). The long term effects may also be dependent on changes to intracortical glutamerigc synaptic transmission. The effects of long term tDCS on neuronal membrane voltage are suggested to induce alterations to expression of the N-methyl-D-aspartate receptors (NMDA) a post synaptic glutamate receptor. The NMDA antagonist dextromethorphane attenuates the long-term increases in corticospinal excitability after anodal tDCS, whilst the NMDA agonist d-cycloserine prolongs the long-term increases in cortical excitability (Nitsche et al., 2003b, 2004). Although the effects of tDCS on GABAergic transmission are less clear, there is some evidence that GABA levels may also be affected by long term tDCS. Stagg et al. (2009) used magnetic resonance spectroscopy to examine *in vivo* neurotransmitter concentrations after both anodal and cathodal tDCS of motor cortex. They reported that anodal tDCS reduced concentrations of the inhibitory neurotransmitter GABA, whilst cathodal tDCS reduced both glutamate and GABA. Using epidural recordings of descending volleys elicited by TMS in anesthetised patients Lang et al. (2011) reported facilitation of I-waves following five minutes of anodal motor cortex tDCS. I-waves are thought to be intracortical in origin (Di Lazzaro and Rothwell, 2014), supporting the suggestion that long term tDCS elicits changes to intracortical synaptic function.

Based on these findings, it is assumed that long-term changes to cortical excitability after tDCS may be due to mechanisms similar to Hebbian long term potentiation (LTP) and long term depression (LTD) changes in synaptic function (Nitsche et al., 2012). Hebb (2005;1949) proposed mechanisms for cortical plasticity suggests that when one cell (cell A) is in close proximity to another (cell B), and the firing of cell A is consistently involved in the firing of cell B, a metabolic change occurs between the two cells which increases the efficiency with which cell A causes cell B to fire (Hebb, 2005). In accordance with this model, anodal tDCS is suggested to increase NMDA activation, leading to an increase synaptic strength referred to as LTP like plasticity. Conversely, cathodal tDCS is suggested to induce long term depression like plasticity through the hyperpolarisation of the post synaptic membrane and subsequent reduction in NMDA activity (Stagg and Nitsche, 2011).

Long-term tDCS induced changes to synaptic function result in related activity changes to interconnected brain regions. Using positron emission tomography, Lang et al. (2005) reported changes to cerebral blood flow (CBF) in both ipsi and contra lateral cortical and sub-cortical regions following motor cortex tDCS. There were increased CBF changes in the contralateral motor cortex, the anterior cingulate cortex, the right parietal occipital junction, the superior temporal junction and the cerebellum. These changes were polarity dependent with different increases and reductions in excitability occurring after each stimulation (Figure 12).

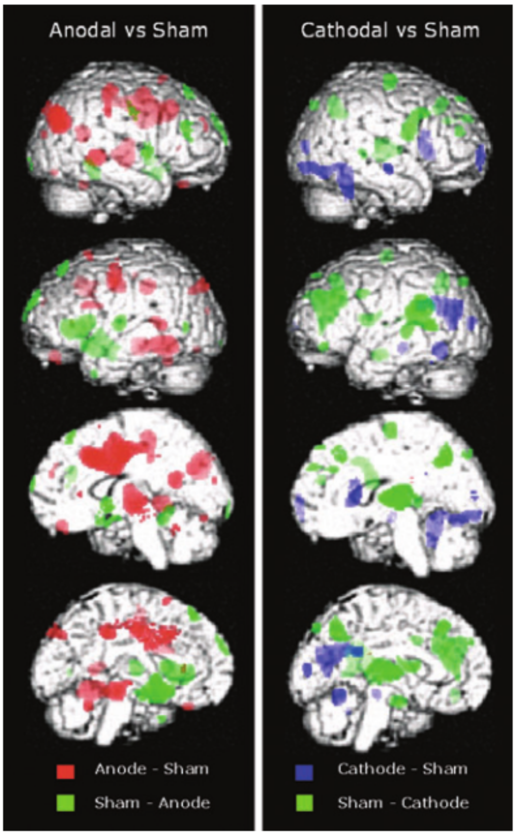

Figure 12.Increases and decreases in CBF after tDCS. Both anodal (left hand plot) and cathodal (right) tDCS show changes, relative to sham stimulation. From Lang et al. (2005).

Using electroencephalography Polanía et al. (2011) and colleagues reported that anodal motor cortex tDCS (10 minutes, 1 mA, cathode over contralateral supraorbital area) increased synchronization in alpha frequency in frontal and parietal areas, high gamma frequency) band in motor-related regions. These effects were greater during voluntary hand movements than when at rest. Using fMRI the same group (Polanía et al. 2012; Polanía, Paulus, et al. 2011) changes in functional connectivity after motor cortex tDCS. Anodal tDCS (10min at 1 mA) increased functional connectivity with prefrontal cortex and cingulate cortex, as well as sub cortical structures including the thalamus and striatum.

2.4.4 Inter-Individual Variability in Physiological Responses to tDCS

Early reports of the physiological effects of tDCS predominantly described dichotomous polarity dependent effects, whereby anodal and cathodal tDCS increased and decreased neuronal excitability respectively (Nitsche and Paulus, 2000, 2001). Though these effects were replicated several times, using a variety of stimulation parameters, there were some reported failures to replicate canonical (anodal-excites\cathodal-inhibits) effects (Jacobson et al., 2012). A meta-analysis of reported tDCS effects revealed the probability of achieving the canonical modulation of excitability was only 0.67 (Jacobson et al., 2012). López-Alonso et al., (2014) measured MEP amplitude after 1 mA tDCS of motor cortex and reported that anodal tDCS increased MEP amplitude in only 45% of participants whilst the remainder responded in the opposite manner, where anodal tDCS reduced MEP amplitude. Wiethoff et al., (2014) examined the effect of 2 mA anodal and cathodal tDCS of motor cortex on MEP amplitude. They reported that anodal tDCS increased MEP amplitude in approximately 75% of participants, whilst cathodal tDCS reduced MEP amplitude in 60% of participants. However, they also reported that only 36% of participants responded to both forms of tDCS in the canonical anodal-cathodal manner. In 21% of participants anodal tDCS inhibited and cathodal tDCS increased MEP amplitude, whilst in 38% of participants both anodal and cathodal tDCS increased MEP amplitude.

Both computational modelling and experimental data have highlighted the impact of anatomical and physiological variation on tDCS effects. Variation in brain structure, skull thickness, cerebral spinal fluid, sub cutaneous fat, genotype, neurotransmitter balance and neural circuit organisation have all been proposed to influence tDCS effects (Opitz et al., 2015; Truong et al., 2013; Datta et al., 2009; Nieratschker et al., 2015; Lang et al., 2011; Krause et al., 2013, 2014; Datta et al., 2012). The initial 'state' of the target neurons prior to stimulation may also mediate the effects of tDCS (Krause et al., 2013, 2014; Datta et al., 2012). Unfortunately, neither Wiethoff et al., (2014) or López-Alonso et al., (2014) included a sham condition, so it is not clear as to what extent the variability seen here may be due to factors other than simply response to tDCS, for example the variability in the measurement of corticospinal excitability by TMS. Nonetheless, it is clear that inter-individual differences in the response to tDCS may limit its application as an investigative tool. Understanding these individual differences is essential when interpreting the effects of tDCS on cognition and motor responses (Horvath et al., 2014a) however, as yet there is no established way to predict an individual's response to tDCS (López-Alonso et al., 2014).

2.4.5 The Physiological Effects of Prefrontal tDCS

Unsurprisingly, given relative ease with which changes in excitability can be measured using the TMS induced MEP, much of the work describing physiological effects of tDCS has used motor cortex stimulation (Stagg and Nitsche, 2011). However, both modelling and imaging data reveal similar effects with prefrontal stimulation. Using electroencephalogram (EEG), Keeser et al., (2011b) reported that anodal prefrontal tDCS reduced delta and increased beta wave, indicating increased excitability analogous with results reported in motor cortex. tDCS of prefrontal cortex is also suggested to modulate the activity in a number of widespread cortical networks. However, results are somewhat contradictory. Peña-Gómez et al., (2011) reported the anodal prefrontal tDCS increased connectivity between prefrontal cortex and parietal cortex, a network that has been shown to be involved in dual-task performance (Collette et al., 2005), and Keeser et al., (2011) have reported that prefrontal tDCS modulates both ipsilateral and contralateral frontal-parietal connectivity. Stagg et al., (2013) reported anodal tDCS of the left prefrontal cortex increased measures of regional blood perfusion in structurally connected areas including the primary sensory cortex and the left parietal cortex whilst cathodal tDCS reduced perfusion in the thalami.

2.4.6 tDCS of Prefrontal Cortex and Cognition

Because of its capacity to modulate activity at both the stimulation site and across distributed neural networks (Meinzer et al., 2012), a large number of studies have examined the effects of tDCS on cognition. A number of researchers have examined the effects of tDCS on working memory: Fregni et al., (2005) reported that 1 mA of anodal prefrontal tDCS improved accuracy in the n-back working memory task. Subsequently, Boggio et al., (2006) reported that 2 mA of anodal prefrontal tDCS improved working memory performance in Parkinson’s disease patients. Positive effects of anodal tDCS on working memory accuracy were subsequently reported in healthy adults (Teo et al., 2011; Hoy et al., 2013; Gladwin et al., 2012) older adults (Berryhill and Jones, 2012) and stroke patients (Jo et al., 2009). Gladwin et al., (2012) tested the effect of anodal tDCS on working memory using a delayed response memory task (the Sternberg task) with a distracter task during the delay in order to assess the ability to selectively attend to items. They reported that, compared to sham stimulation, anodal tDCS improved selective attention, that is, the allocation of attention to relevant task stimuli. These studies show that prefrontal dependent cognitive functions can be enhanced with anodal tDCS, and support prior brain imaging studies which show prefrontal cortex activation during executive function tasks (Wager and Smith, 2003; Owen et al., 2005).

2.4.7 Models of tDCS Effects on Cognition

Early reports described a polarity dependent effects on behaviour analogous to the early reports of motor cortex excitability changes after stimulation, where anodal tDCS improved prefrontal cortex dependent cognitive functions (Boggio et al., 2006; Fregni et al., 2005). However, as with the physiological effects of tDCS, there also appears to be some variation in the behavioural consequences of stimulation. Both facilitation and reductions in cognitive task performance have been reported following both anodal and cathodal tDCS (Weiss and Lavidor, 2012; Jacobson et al., 2012) and there appears to be significant variation in behavioural responses to a number of stimulation parameters (Tremblay et al., 2014). In addition, even in cases where tDCS facilitates cognitive performance in one task, it may result in decrements in another (Tremblay et al., 2014). Accordingly, several models have now been proposed to explain the effects of tDCS on behaviour, incorporating both individual variation and paradoxical facilitation after cathodal stimulation.

The zero sum model of tDCS was proposed by Brem and colleagues (2014). Zero-sum is a concept from game theory, wherein a player’s losses or gains are balanced by gains, or losses, for other players, resulting in a sum of zero (Brem et al., 2014). Brem and colleagues (2014) suggest that the brain is a closed system with finite processing resources. Accordingly, ‘gains’ or alterations in neural processing or cognitive function must be accompanied with losses in other structures or functions, in order for the demand on resources to remain stable (Brem et al., 2014). The zero-sum concept provides a useful framework against which both facilitative and inhibitive tDCS can be interpreted. Whilst the notion that the whole brain can be considered a closed system with finite resources has been challenged (Luber, 2014), the zero-sum framework may be applicable to executive functions, which appear to be have a finite capacity (Luber 2014). However, the model still presumes there will be a uniform response to stimulation (i.e. anodal prefrontal stimulation improves *x*, but impairs *y*) which may not reflect the reported inter and intra-individual variability in response to stimulation (Wiethoff et al., 2014; Tremblay et al., 2014).

Krause and colleagues (2013) propose that tDCS modulates the cortical excitatory/inhibitory balance. Long-term tDCS is suggested to influence cortical activity through alterations to glutamergic and GABAergic transmission (Stagg et al., 2009; Stagg and Nitsche, 2011) and thus the stimulation effects may be dependent on individual expression of these (and other) excitatory and inhibitory neurotransmitters, accounting for inter-individual response to stimulation protocols (Krause et al., 2013). Under the excitation/inhibition framework, paradoxical facilitation following cathodal tDCS would result from a readjustment in a excitation dominant excitation/inhibition balance (Krause et al., 2013). However, baseline task performance characteristics, suggested to represent the 'state' of the neuronal populations involved in task performance, appear to influence stimulation effects (Tseng et al. 2012; Learmonth et al. 2015; Benwell et al. 2015). Under these circumstances, excitation/inhibition balance may be less important than activation state of the neurons being stimulated.

Miniussi et al. (2013) have proposed a stochastic resonance model to explain the state dependent effects of tDCS. The stochastic resonance model assumes that biological systems have a measurement threshold, altered by a signal to noise ratio of a given input (Stocks, 2000). The performance of such a system depends on its ability to identify signal from noise (Miniussi et al., 2013). tDCS is suggested to inject noise into neural systems, whether this noise facilitates or reduces the ability of the system to differentiate signal form noise depends on the underlying state of the given system, and how close to the measurement threshold the input (signal+ noise) is (Miniussi et al., (2013), Figure 13 for an example). The stochastic resonance model thus provides a useful framework for interpreting the influence of task performance characteristics on tDCS effects.

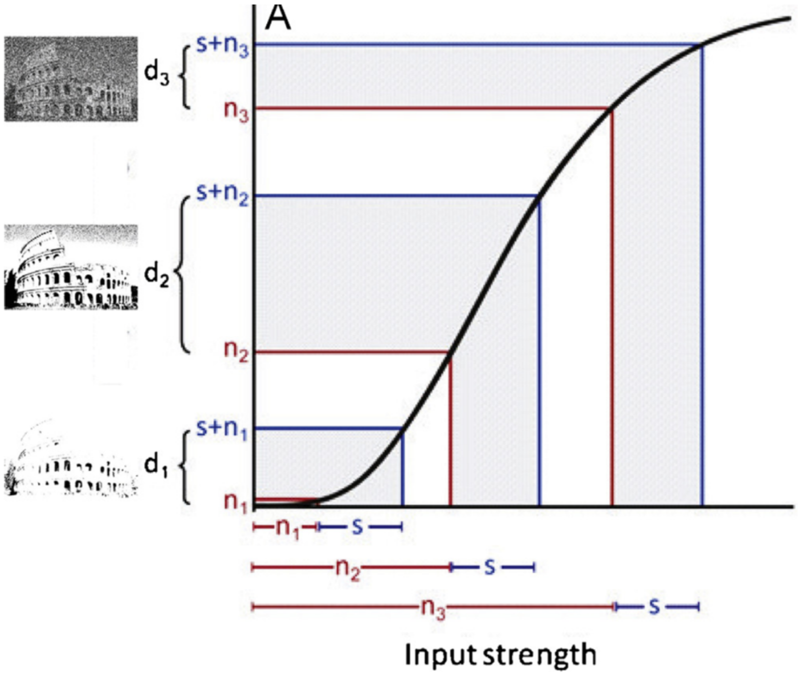

Figure 13. An example of stochastic resonance effects. The effect of an injection of noise into the neural system is dependent on the input strength (signal + noise) of the system. In a system with a sub-measurement threshold input strength (d_1) an injection of noise from tDCS (n_2) increases input strength above measurement threshold, improving the ability of the system to differentiate signal from noise and thus improves signal processing (d_2). However, when input strength is at measurement threshold, injection of noise from tDCS (n_3) increases input strength to an extent where the system's ability to discriminate signal from noise is impaired (d_3). From Miniussi et al (2013).

2.4.8 tDCS and Dual-Task Performance

Dual-task performance is suggested to activate a neural network which includes prefrontal cortex (Collette et al., 2005; Chmielewski et al., 2014). As prefrontal tDCS changes the activity of functionally connected neural networks (Meinzer et al., 2012; Stagg et al., 2013) it may thus present a suitable tool to evaluate the contribution of prefrontal cortex to the control of dual-task performance (Filmer et al., 2014). Filmer *et al*., (2013) examined the effect of anodal and cathodal tDCS of left prefrontal cortex on the ability to divide attention across two simultaneously performed visual and auditory tasks. They reported that, relative to sham stimulation, cathodal but not anodal tDCS reduced reaction times. In accordance with Weiss & Lavidor (2012), they suggest that cathodal tDCS induced inhibition allows a more efficient processing of task relevant stimuli. If the role of prefrontal cortex during the dual-task is to attend to and process only the task relevant signals

(Miller and Cohen, 2001), inhibition of prefrontal cortex thus appeared to reduce the input signals from task irrelevant processes (signals not related to the auditory and visual tasks), increasing the participants' capacity to attend to the multiple, task relevant, signals. However, the physiological validity of the improved neural efficiency the concept has been questioned. Bestmann et al., (2014), suggest that there is no neurobiological basis for such an assumption, and that efficiency based explanations are simply post hoc explanations for unexpected effects. Nonetheless, this finding supports the suggestion that prefrontal cortex is involved in the control of dual-task performance, and that said performance can be influenced by tDCS.

Only one study has examined the effect of tDCS on dual-task gait. Zhou et al., (2014) reported that, compared to sham tDCS, anodal prefrontal tDCS reduced the dual-task cost on gait speed. They reported no effect of tDCS on STV or on performance in the cognitive task. Zhou et al., (2014) suggest that anodal tDCS improves the ability to attend to multiple stimuli (in this case gait and a cognitive task) analogous to an increase in the capacity of the central limiting dual-task resource. However, Zhou et al (2014) did not assess the effect of cathodal tDCS on dual-task gait, which allows for more causal conclusions to be drawn about the involvement of cortical areas to behaviour (Vines et al., 2006) and may also improve dual-task performance (Filmer et al., 2013). Participants also appeared to perform at ceiling in the cognitive task (serial subtractions in threes), which Zhou et al., (2014) suggests occurred due to the relative ease of the task, and which may have prevented any reductions in task performance following anodal stimulation. Thus, although it may appear as if anodal tDCS increased the capacity to divide attention across two tasks, it may simply have increased the allocation of resources to gait performance. Because the cognitive task was 'easy' there was no decrement in task performance after reallocation of the cognitive control resources. In addition, dual-task performance is mediated by a number factors including task difficulty and the nature of the walking task, all of which may influence task prioritisation and performance (Yogev- Seligmann et al., 2012). In order to fully understand the role of prefrontal cortex in the control of dual-task gait, polarity and task dependent influences on dual-task gait, and tDCS effects, must be examined.

In summary, tDCS provides a novel method by which the neural correlates of behaviour can be examined. tDCS is suggested to modulate neural membrane potential, causing long term (up to one hour) alterations in synaptic activity, which may be related to changes in NMDA expression. As such, the effects of tDCS as suggested to analogous with Hebbian mechanisms of plasticity. A large and growing number of studies have reported changes in cognitive task performance following prefrontal tDCS. Only one study has examined the effect of prefrontal tDCS on dual-task gait, and reported a facilitative effect of anodal tDCS on walking speed. However, it is not clear yet what role prefrontal cortex plays in the cognitive control of dual-task gait. By manipulating current polarity to differentially increase or reduce prefrontal cortex excitability, as well as investigating the effects of tDCS on task prioritisation during dual-task gait performance, it may be possible improve understanding of the relationship between cognitive control, gait and prefrontal cortex.

2.5 Aims and Hypotheses

The ability to divide attention during walking is examined using a dual-task gait paradigm wherein the walker simultaneously performs a cognitively demanding task (Yogev-Seligmann et al., 2008). During dual-task gait, performance in one or both tasks is usually impaired (Al-Yahya et al., 2011). Theories of the dual-task effect posit that this cost occurs due to increased demand on a limited capacity central resource (Tombu and Jolicœur, 2003). prefrontal cortex is frequently suggested to be a part of this central resource (Yogev-Seligmann et al., 2008) and imaging evidence suggests prefrontal cortex is more active during dual-task gait (Holtzer et al., 2011). Prevalent theories of prefrontal cortex function indicate that it is part of a cognitive control network involved in the bias and prioritisation of task relevant neural processes (Miller, 2000). However, the role of prefrontal cortex in the control of dual-task gait is unknown. tDCS is suggested to be a method by which the neural correlates of behaviour can be examined (Filmer et al., 2014). Therefore, the aim of this thesis was use tDCS to examine the role of prefrontal cortex in the control of dual-task gait. In order to meet this aim, four experiments were carried out. The individual aims and hypotheses for each experimental chapter are detailed below:

Chapter 4: Effect of cognitive task type and walking speed on dual-task gait in healthy adults

Aim: To compare the role of cognitive task type and walking speed on dual-task gait performance

Hypotheses: Dual-task gait performance would be mediated by the nature of both the walking task (speed) and cognitive task (task type).

Chapter 5: Effect of transcranial direct current stimulation on task processing and prioritisation during dual-task gait.

Aim: To examine the role of prefrontal cortex in the control of dual-task gait using anodal and cathodal tDCS

Hypotheses: Prefrontal tDCS would influence the processing of one task over the other during dual-task gait, and that these effects would be mediated by walking speed.

Chapter 6: Effect of prefrontal cortex tDCS on corticospinal excitability and cognitive task performance

Aim: To replicate reported effects of prefrontal tDCS on cognitive task performance and corticospinal excitability (Fregni et al., 2005; Vaseghi et al., 2015a) and to investigate the relationship between these effects.

Hypotheses: Anodal tDCS would improve working memory performance, whilst cathodal tDCS would reduce corticospinal excitability. There would be a relationship between the physiological and behavioural effects of tDCS, as reported elsewhere (Bortoletto et al., 2015).

Chapter 7: Effect of prefrontal tDCS on dual-task gait performance is dependent on walking modality and task difficulty

Aim: To examine whether the effects of tDCS on dual-task gait performance were dependent on the walking modality and relative task difficulty.

Hypotheses: The dual-task cost on gait would be higher during over-ground walking than during treadmill walking, and these differences would mediate the effects of tDCS on dual-task gait. Additionally, perceived task difficulty, which may represent underlying neural states during task performance, would also mediate tDCS effects on dual-task walking.

3. General Methods

This section describes the materials and methods used in the experimental chapters of this thesis.

3.1 Health and Safety

All procedures in the experimental chapters of this thesis were approved by the University of Brighton ethics committee. All experiments were performed within the Welkin Human Performance Laboratories, University of Brighton, Eastbourne. All brain stimulation experiments were carried out with two experimenters present. Participants with medical contra-indications to brain stimulation protocols were excluded from the study as a safety precaution. No adverse effects resulting from tDCS were reported by participants. All experimental procedures underwent full risk assessments, outlining the potential hazards, likelihood of hazards occurring, individuals at risk and control procedures to reduce the probability of the hazard from occurring. There was a first aid trained experimenter in attendance at all times.

3.2 Participants and Recruitment

Participants were recruited from within the student body of the University of Brighton and from members of the community. Before each study, experimental procedures were outlined to the participants, and each participant gave written informed consent stating that they agreed to take part. Medical contra-indications to tDCS (Chapter 5, 6, 7) and TMS (Chapter 6, 7) were assessed using a medical questionnaire (Appendix 1). Contra-indications to stimulation were identified using the recommendations of Rossi et al. (2009) and Poreisz et al. (2007) and included: pregnancy, a history of cardiovascular disease, chronic migraines and headaches, history of neurosurgical procedures, epilepsy, hearing or vision issues, a history of psychiatric disease and surgically implanted metal in the head or neck (see medical questionnaire, Appendix 1). For participant recruitment in Chapter 5 and 6, an *a-priori* power analysis was performed using the GPower analysis software (version 3.1.9.2, Faul et al. (2007)), using data on the effects of tDCS on a cognitive task reported in a previous study (Fregni et al. 2005). As the effect size was not explicitly reported, an estimate was calculated from the reported *T* and *N* (Lakens, 2013;

Lakens and Evers, 2014). The estimated effect size (d_z) = 0.88. Using an α=.0.5, it was estimated that ten participants would be required (power=0.80).

3.3 Familiarisation

All participants were familiarised with tDCS (Chapter 5, 6, 7), the cognitive tasks (all experimental chapters), TMS (Chapter 6, 7) and the walking protocol (Chapter 4, 5, 7). In Chapter 4, 5 and 7, participants' preferred treadmill walking speed was calculated during familiarisation by repeating the following protocol twice: Starting at a speed of 2.0 km.h^{-1}, participants walked on a motorised treadmill (Life fitness CLST, Life Fitness, Cambridge, UK). Treadmill speed was increased in 0.1 km.h^{-1} increments until the participant reported that the speed equalled their preferred walking speed. Participants were blind to the treadmill speed. The treadmill speed was then increased to 6.5 km.h^{-1} and lowered in 0.1 km.h^{-1} increments until the participant again identified their preferred speed. The mean of the four reported walking speeds was recorded as preferred walking speed.

3.4 Gait Analysis

Gait analysis (Chapters 4, 5 and 7) was carried out using a portable body worn gait analysis system (OPAL, APDM, Portland, USA) which is comprised of three sensors: one placed on each shank (4 cm superior and anterior to the malleolus) and one on the lumbar spine (at the L5 vertebrae, identified by palpating the lumbral sacral joint). Each sensor contains a three-axis piezoelectric gyroscope with a range of $\pm$2000 deg.s^{-1} sampling at 128 Hz. Before each study gyroscope calibration was performed in accordance with the manufacturer's instructions using the Mobility Lab software (version 1.0, APDM, Portland, USA). Signals from the gyroscopes were transmitted wirelessly to a personal computer running Mobility Lab where they were low pass filtered and underwent bias removal and were recorded for offline analysis.

Two temporal-spatial gait parameters were recorded: stride time and trunk range of motion (RoM). Stride time (s) is the time between successive heel strikes of the same leg (Winter, 1991). The Mobility Lab system derives stride time from the angular acceleration of the shank gyroscopes using the an established algorithm (Salarian et al. 2004). Mid-swing is first identified as a peak in angular velocity over 50 deg.s^{-1} (Figure 14). The initial contact area and terminal contact area are then subsequently identified: initial contact area as the first peak of negative angular shank velocity preceding mid-swing, terminal contact area was identified as the negative angular velocity peak prior to swing phase initiation (Figure 14).

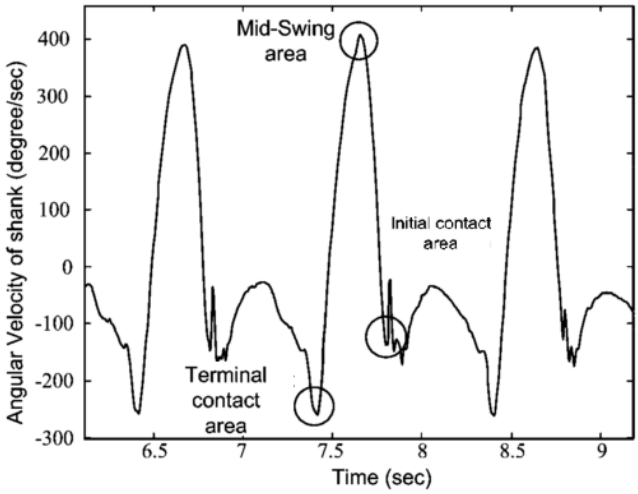

Figure 14. Example of the shank angular velocity trace with gait identification events marked. Adapted from Salarin et al. (2004)

The algorithm (Salarian et al., 2004) identifies five associated time events: initial contact of the right foot (IC_R), terminal contact of the left foot (TC_L) initial contact of the left foot (IC_L) and terminal contact of the right foot (TC_R). Gait cycle time for each leg is then calculated using the following equation for the kth gait cycle (equation is for the right leg):

Equation 1. Gait cycle time (Salarian et al., 2004)

$$\mathrm{GCT}k = \mathrm{IC_R}\ (k+1) - \mathrm{IC_R}\ (k)$$

Mean gait cycle time for both legs across all gait cycles is then recorded as stride time. STV was calculated as the coefficient of variation of stride time across all gait cycles using the following equation (Hausdorff, 2005):

Equation 2. Calculation of stride time variability

$$STV = \left(\frac{Standard\ Deviation}{Mean}\right) \times 100$$

The Mobility Lab system identifies trunk range of motion (RoM) in the mediolateral and anterior-posterior directions during gait using a cumulative trapezoidal numerical integration of the trunk and shank gyroscope data, which results in a measure of angular distance (deg) covered by the trunk gyroscope over each gait cycle.

3.4.1 Validity and Reproducibility of the Mobility Lab System

Aminian et al. (2002) assessed the validity of the estimation of gait cycle time by shank mounted gyroscopes against the estimation of gait cycle time by foot switches. They reported a correlation of $r>0.99$ and a mean standard error (calculated using the root mean square error) of 8 ms [95% CI 7-13ms] between both techniques. Salarian et al. (2004) reported a mean error (difference) of 2.2 ± 23 ms between the estimation of gait cycle time using shank gyroscopes and a VICON 3D motion capture system, and Aminian et al. (2004) reported a mean error (difference) in gait cycle time estimation between gyroscopes and a fixed force platform system of 0.3 ± 24.6 ms, though neither provided any other statistical analysis of validity. Greene et al. (2012) compared the estimation of gait cycle events (initial contact and terminal contact) using shank gyroscopes with that of the GAITrite force carpet: they reported a mean error (difference) of 28.95 ± 6.98 ms in the identification of initial contact and a mean error of 5.90 ± 29.67 ms for the identification of terminal contact. They also reported a mean difference of 6.69ms for the estimation of gait cycle time. Interclass correlations (ICC) for gait cycle time estimation between the two techniques was 0.98 which has previously been suggested as representing excellent validity in gait analysis systems (Bilney et al., 2003). Mancini et al. (2012) also reported significant correlations between postural RoM measured with Mobility Lab against those measured with a force platform. The estimation of spatial gait parameters using shank gyroscopes has been shown to be sensitive to changes in walking speed in healthy adults (Greene et al., 2012) and pathological changes to gait in older adults (Aminian et al., 2002) and in patients with Parkinson's disease (Salarian et al., 2004).

The between trial measurement error of the estimation of stride time, STV and trunk RoM by the Mobility Lab system was calculated using data from Chapter 4. 10 right handed males visited the laboratories on two occasions, separated by at least 48 hours. Stride time (s) and STV (%) were recorded using the Mobility Lab system during treadmill walking for two minutes during both single task (just walking) and dual-task (walking whilst counting backwards in seven from a number between 590-

600). Differences in STV and trunk RoM between each visit were assessed using a two tailed paired sample Student's t test with statistical significance set at $p<0.05$. Absolute and relative reliability was assessed with mean bias, typical error of the measurement (TEM) and ICC. TEM was calculated using the following equation:

Equation 3. Typical error or the measurement for stride time variability

$$TEM = \left(SD(diff) \div \sqrt{2}\right)$$

Where SD (diff) is the standard deviation of the mean difference between the two scores. TEM was expressed in both units of measurement. Results from the statistical analysis are displayed in table 1.

Table 1.Reproducibility of the OPAL system

	Mean Bias	T-Test Sig	TEM	ICC
Stride time	0.01 s	0.139	0.01 s	0.99
Stride Time Variability	0.05 %	0.405	0.15 %	0.89
Mediolateral trunk RoM	0.35 deg	0.673	1.82 deg	0.64
Anterior-posterior trunk RoM	0.20 deg	0.405	0.52 deg	0.90

RoM = Range of Motion

For all gait parameters, there were no significant ($p<0.05$) differences between the two trials. Previous studies examining the reliability of gait analysis systems have suggested that ICC's over 0.83 are acceptable limits for the estimation of temporal gait parameters in young adults (Bilney et al., 2003). Using these limits as a guideline, the Mobility Lab system can be said to reliably estimate stride time, stride time variability and anterior-posterior trunk RoM. The ICC for mediolateral trunk RoM was below the accepted range, and changes in this parameter must be interpreted with caution. As the ICC may not fully take into account individual variability, it is recommended to include absolute measures of reliability, such as TEM (Atkinson and Nevill, 1998). Interpretation of the changes in STV and trunk RoM in this thesis thus account for the TEM.

3.5 Cognitive Tasks

Two cognitive tasks were used in the experiments in this thesis: in Chapters 4 and 6, the N-Back (2-Back) working memory task was used and in Chapters 4, 5 and 7, a serial subtraction task was used. The 2-back working memory task was programmed using the DMDX software (University of Arizona, Tucson, USA) on a personal computer. Participants were presented with a sequence of 100 (in Chapter 6) or 50 (in Chapter 4) letters (A-H) in a pseudo-randomised order. The letters were presented in white text against a black background, and were displayed for 500ms with an inter-stimulus interval of 2000 ms. In Chapter 6, there were 20 target stimuli in the 100 letter set whilst in Chapter 4 there were 10 target stimuli in the 50 letter set. The letters were displayed sequentially, and participants were asked to respond by pressing a key on a computer keyboard (Chapter 6) or pressing a button on a handheld infrared mouse (SP400, Duronic, London, UK, Chapter 4). A response was required when the letter displayed on the screen matched the letter displayed two stimuli previously ("2-back"). The number of correct answers and the number of errors (missed targets and incorrect responses) were recorded by DMDX and analysed off-line. In Chapter 6, the error ratio was calculated for the 2-back test using the following equation:

Equation 4. Error ratio (%) for 2BACK

$$\left(\frac{Number\ of\ errors}{Total\ Number\ of\ Possible\ Responses}\right)\times 100$$

During the serial subtraction task, participants were asked to subtract in sevens starting from a number between 591-595 (Chapter 4 and 5) or between 1500 and 1100 (Chapter 7). The starting number was increased to a four-digit number in Chapter 7 because two participants in previous studies reached 0 when counting backwards from 591. Participants were asked to accurately count back as many numbers as possible for 120 s. In Chapter 4, responses were recorded on the Audio Memos software package (version 3.6, Imesart, Luxembourg) on a tablet computer (iPad, Apple, Cupertino, USA). In Chapter 6, responses were recorded using a portable digital dictaphone (UX200, Sony, Tokyo, Japan). In Chapter 7, responses were recorded using the Videography software package (Appologics, Eurasberg, Germany) running on a tablet computer (iPad, Apple, Cupertino, USA) which was synchronised to the gyroscope data through Mobility Lab. The video was analysed offline using the Premier pro software package (Version CS5, Adobe, San Jose, USA). Number of correct answers and errors were recorded and analysed offline. The error ratio (all chapters) was calculated using the following equation:

Equation 5. Error ratio for serial subtraction task

$$\left(\frac{Number\ of\ errors}{Number\ of\ correct\ answers}\right)\times 100$$

3.6 Transcranial Direct Current Stimulation

Transcranial stimulation was delivered via a programmable battery driven stimulator with a maximum stimulator intensity of 2 mA (HDCkit, Newronika, Milan, Italy). The HDCKit is comprised of two modules: a stimulation box (HDCstim) and a programming box (HDCprog). The stimulation box can be programmed prior to stimulation, and does not display whether the stimulation is active (anodal or cathodal) or sham. The connections between HDCstim and the electrodes were concealed, preventing identification of the polarity direction (anodal or cathodal). In all studies, the stimulator was programmed by a technical member of staff not involved in the study, and both participant and experimenter were blind to the stimulation condition. tDCS was delivered via two rubber electrodes placed in saline soaked sponge covers, themselves covered in a conductive gel. The electrodes were held in place using an elasticated hair net

The active electrode was 35 cm^2 in size whilst the reference electrode was 72 cm^2 in size. In accordance with the study of Zhou et al., (2014) the applied current in all experiments was 1.5 mA, giving a current density of 0.043 mA/cm^2 under the active electrode and 0.021 mA/cm2 under the reference electrode. A larger reference electrode reduced current density preventing confounding effects from stimulation of the reference site (Nitsche et al., 2008). Stimulation of this duration leads to long term changes to cortical excitability lasting for up to 60 minutes (Nitsche and Paulus, 2001). In order to blind subjects to the stimulation condition (Gandiga et al., 2006) and to reduce discomfort, the current was ramped up for 15s in all conditions. Subsequently, stimulation was applied for 15 minutes for the active (anodal and cathodal) conditions whilst for the sham condition the current was switched off after

90s. In order to reduce possibly confounding effects of priori brain state on cognition, participants were asked to sit quietly during the stimulation period.

Electrode placement for prefrontal tDCS was determined using the 10-20 EEG system (Herwig et al., 2003). In all chapters, the active electrode was placed over F3, whilst the reference electrode was placed over FP2 (Figure 15).

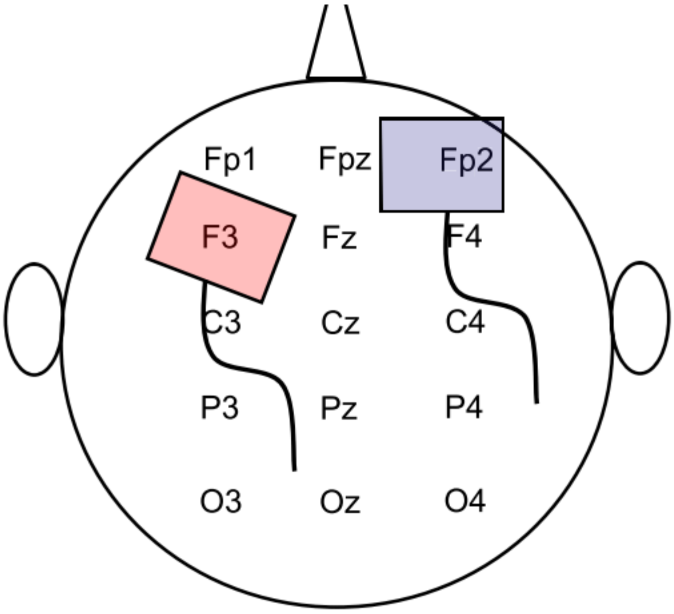

Figure 15. Electrode placement according to the 10-20 EEG system. Adapted from (Nitsche et al., 2008)

This electrode montage has been reported to alter prefrontal cortex dependent cortical activity and cognitive function in a number of studies (Kuo and Nitsche, 2012; Tremblay et al., 2014; Keeser et al., 2011b).

3.7 Transcranial Magnetic Stimulation

Assessment of corticospinal excitability (Chapter 6, 7) was performed using single pulse TMS, delivered using a Magstim^{200} stimulator which has a maximum output of 2.5 Tesla (Magstim Company, Whitland, UK). During TMS, a high current pulse is briefly produced in the magnetic coil, comprised of one or more copper windings. During stimulation, a magnetic field is produced perpendicularly to the plane of the coil. An electric field is induced perpendicularly to the magnetic field which excite neural tissue (Hallett, 2007). When motor cortex is stimulated, the induced electrical fields, if of sufficient strength, results in both direct and pre-synaptic activation of corticospinal neurons (Di Lazzaro, 2004). Unless delivered at relatively high intensities, motor cortex TMS predominantly results in synaptic activation of corticospinal neurons, resulting in corticospinal volleys referred to as I-waves (Di Lazzaro, 2004). In Chapter 6 and 7, TMS was applied with a flat figure of eight coil (7 cm diameter) placed tangentially to the scalp and at an angle of 45° to the midline. This coil angle preferentially results in cortico-cortico activation of corticospinal tract neurons (Di Lazzaro and Rothwell, 2014). When delivered to motor cortex TMS volleys travel down the corticospinal tract and result in activation of the spinal motoneurons and peripheral muscles (MEP). The amplitude of the MEP can be used to determine the excitability of the corticospinal system (Hallett, 2007).

In both Chapter 6 and 7, TMS was applied to the representation of the first dorsal interosseous (FDI). Correct coil placement determined was using the following method: after marking the vertex (Cz in the 10-20 EEG system), the "hotspot" for TMS was identified as the area of left motor cortex which when stimulated using a stimulator intensity of 60% of maximum, resulted in the largest MEP amplitude, as measured by surface electromyography (EMG) in the left FDI. All stimulations were delivered with the coil placed at this hotspot. Subsequently, the stimulator intensity which resulted in an EMG response of below 0.05mV in five of ten stimulation (resting motor threshold) was determined by decreasing stimulator intensity in 1% increments from 80% of maximum stimulator output (Rossini et al., 1994). All subsequent TMS were delivered at 120% of the resting motor threshold. This stimulator intensity is frequently used to asses corticospinal excitability changes following tDCS (e.g Bastani and Jaberzadeh, 2013) and is suggested to preferentially activate I-waves (Di Lazzaro and Rothwell, 2014).

3.7.1 Electromyography

Peak to peak MEP amplitude (mV) in the FDI were recorded and analysed off-line using the Labchart software package (Labchart version 7, ADInstruments, Dunedin, New Zealand). Electrode placement was determined using index finger abduction to identify the FDI using a belly tendon montage, and placement was confirmed by visual examination of EMG response during maximal contraction. The ground electrode was situated in the right ulna styloid process. All EMG signals were band pass filtered (2-20 kHz), amplified (x 1000) and sampled at 4 kHz. Data were collected via a Power lab analogue-digital interface (26t ADInstruments, Australia).

3.8 Data Analysis

All data are presented as mean +SD unless otherwise stated.

In addition to the absolute value for STV, trunk RoM and error ratio, the dual-task cost on each variable was calculated. The dual-task cost expresses the absolute value relative to the value during single task performance, providing a more sensitive indication of changes to cognitive control under different dual-task gait conditions (Kelly et al., 2010). In Chapter 5 and 7, the dual-task cost on STV and trunk RoM (Chapter 5) were calculated using the below equation:

Equation 6. The dual task cost on STV and Trunk RoM.

$$\left(\frac{(Dual\ task\ - Single\ task)}{Single\ task}\right) \times 100$$

Because error ratio could equal 0, the dual task cost on error ratio was calculated using the following equation:

Equation 7. The dual task cost on error ratio.

$$(Dual\ task - Single\ task)$$

3.8.1 Statistical Analysis

All data were analysed using the SPSS statistical package (version 20, IBM, New York, USA). Data were checked for normality and sphericity. Based on the recommendations of Tabachnick & Fidell (2007) non-Gaussian data were transformed using log and square root transformations and reflected log and square root transformations after examination of skewness and kurtosis using absolute statistics and histograms. Data that violated Mauclhy's test of sphericity were adjusted using the Hyun-Felt method.

Differences in parametric data were analysed using repeated measures ANOVA with Bonferroni correct pairwise comparison follow ups. Non-parametric data were analysed using Freidman's ANOVA with Bonferroni-corrected Wilcoxon signed rank follow up tests. Based on the recommendations of Lakens (2013), partial eta squared (*ηp*) was used as a measure of effect size for ANOVA main and interaction effect sizes and Cohen’s d_{av} for within subjects repeated measures (d) was used for pairwise comparison effect sizes, whilst *r* was used as a measure of effect size for significant differences identified by Wilcoxon signed rank tests.

4. Effect of Cognitive Task Type and Walking Speed on Dual-Task Gait in Healthy Adults

4.1 Abstract

This study examined whether stride time variability (STV) and trunk range of motion (RoM) are affected by the type of cognitive task and walking speed used during dual-task gait. Participants walked at both their preferred and 25% of their preferred walking speed, and performed a serial subtraction and a working memory task at both speeds. Both dual-tasks significantly reduced STV at both walking speeds, but there was no difference between the two tasks. Trunk RoM was affected by the walking speed and type of cognitive task used during dual-task gait: medio-lateral trunk RoM was increased at the slow walking speed and anterior-posterior trunk RoM was higher when performing the serial subtraction task at the slow walking speed only. The reduction of STV, regardless of cognitive task type, suggests healthy adults may redirect cognitive processes away from gait toward cognitive task performance during dual-task gait.

4.2 Introduction

There is a growing recognition amongst researchers that the control of gait may be sub-served by both automatic and high-level cognitive processes (Yogev-Seligmann et al., 2008). The relationship between cognition and gait performance is typically examined using a dual-task paradigm, where participants perform a cognitive task whilst walking. Impairment of gait performance during dual-task gait is thought to indicate competition between shared resources involved in both cognitive and gait tasks (Al-Yahya et al., 2011; Fraizer and Mitra, 2008; Yogev-Seligmann et al., 2008). Researchers use dual-task gait studies to examine differences in the relationship between cognition and gait in healthy adults and clinical populations (Beauchet et al., 2003; Springer et al., 2006). Within the dual-task gait literature, stride time variability (STV) and trunk motion are used as markers of gait automaticity and stability (Gabell and Nayak, 1984; Winter, 1995; Herman et al., 2010). Although dual-task gait is frequently reported to increase STV and influence trunk motion in healthy adults (Asai et al., 2013; Szturm et al., 2013), others have reported decreases (Lövdén et al., 2008) or no changes to STV or trunk motion

(Laessoe et al., 2008; van Iersel et al., 2007; Springer et al., 2006). One possible cause of this discrepancy is the heterogeneity in both the walking protocols and cognitive tasks used within dual-task gait studies, which may alter the effect of the dual-task on gait and balance (Fraizer and Mitra, 2008; Huxhold et al., 2006).

Cognitive task type has previously been suggested to influence the effect of the dual-task on gait (Beauchet et al. 2005; Doi et al. 2011). A number of studies have reported that concurrent performance of a serial subtraction task increases STV in healthy adults (Doi et al., 2011; Beauchet et al., 2005b; Asai et al., 2013). In contrast, the effect of the N-back working memory task on gait is less clear, with previous studies reporting either no change or decreases in STV (Plummer-D'Amato et al., 2008; Lövdén et al., 2008; Schaefer et al., 2010). Serial subtraction tasks are suggested to place high demands on attentional processes (Ganguli et al., 1990) whilst the N-back test is widely assumed to test working memory capacity (Jaeggi et al., 2010; Owen et al., 2005). Thus, the serial subtraction task may increase STV during dual-task gait because both tasks require, and compete for, shared high-level attentional processes (Yogev-Seligmann et al., 2008). Conversely, Beurskens & Bock, (2012) suggest that, as the N-back test does not increase STV during dual-task gait (Lövdén et al., 2008; Schaefer et al., 2010), the primary cognitive processes used to solve the N-back test are not involved in the control of human locomotion. Therefore, differences in the cognitive processes which underlie performance in both tasks may explain the reported disparity between their effects on gait. Comparing a serial subtraction task and working memory task may provide insight into the nature of the cognitive processes required for the control of dual-task gait, however the effects of these two tasks on dual-task gait has not yet been investigated experimentally.

Walking speed may also influence dual-task gait performance (Beauchet et al., 2009c). STV is higher and trunk range of motion (RoM) in the medio-lateral (ML) and anterior-posterior (AP) directions is lower when walking at speeds slower than preferred walking speed (Jordan et al., 2007; Kavanagh, 2009). Beauchet and colleagues (2009) suggested that increases in stride-to-stride variability when walking at speeds below preferred walking speed may indicate a greater reliance on high-level cognitive processes. Constraining the stepping pattern requires the walker to pay greater attention to foot placement, resulting in increased dual task costs

(Sparrow et al., 2002; Brown et al., 2005). The perceived difficulty of the walking task may also influence the allocation of attention during dual-task gait (Kelly et al., 2013, 2010). Slow walking may thus constrain the natural stepping pattern, making gait more difficult and increasing the attention required for gait performance which causes increases to STV and trunk RoM. Beauchet et al., (2009) suggest that reductions in walking speed may be a confounding factor between dual-task gait studies, making interpretation of the effects of dual-task gait on STV difficult. Therefore, it is important to understand whether the decreasing walking speed influences the effects of dual-task gait automaticity and stability.

Although there is now widespread use of dual-task gait paradigms to assess the relationship between cognition and gait, a number of different walking speeds and cognitive tasks, including N-back and serial subtraction tasks, have been used (Al-Yahya et al., 2011). Differences in dual-task gait performance between clinical groups and healthy adults are used to determine changes in the relationship between cognition and locomotion in disease and old age. It is therefore important to understand the consequences of changes in walking speed and the possible differences in the effects of two frequently used cognitive tasks on dual-task gait performance. The present study had two aims:

The primary aim of this study was to compare the effect of the N-back and serial subtraction cognitive tasks on dual-task gait. Serial subtraction tasks are suggested to test attention and concentration which are thought to share cognitive processes with locomotion (Ganguli et al., 1990; Beauchet et al., 2005b), Conversely, the N-back task primarily places demands on working memory, which may not be limited in the control of locomotion (Beurskens and Bock, 2012). Therefore, it was predicted that the serial subtraction task would have a greater effect on STV, trunk RoM and cognitive task performance during dual-task gait than the N-back task. The secondary aim of this study was to examine the effect of reducing walking speed on STV, trunk RoM and cognitive task performance during dual-task gait. Because slow walking may place increased demands on cognitive systems compared to walking at preferred walking speed (Beauchet et al., 2009c) it was predicted that walking at a slow walking speed would amplify the effects of dual-task on gait and cognitive task performance observed at the preferred walking speed. Because task difficulty is thought to influence dual-task gait performance (Kelly et al., 2013), we also examined whether walking speed affected cognitive task performance and perceived task difficulty during dual-task gait.

4.3 Methods

4.3.1 Participants

Following institutional ethical approval, 22 healthy adults (mean age = 22.7 ± 2.7 years) from within the student body of the University of Brighton took part in this study. Exclusion criteria included known gait dysfunction, neurological conditions, visual impairment and contra-indications to treadmill walking. All participants were experienced in treadmill use and gave written informed consent prior to participating.

4.3.2 Gait Analysis

Using a repeated measures design, participants walked on a motorised treadmill (Life fitness CLST, Life Fitness, Cambridge, UK) under both single and dual-task gait conditions. A motorised treadmill was chosen as it allows the walking speed to be controlled without participants being required to attend to their walking speed (Simoni et al., 2013). Temporal gait parameters were recorded using a portable gait analysis system (OPAL, APDM, Portland, USA). The system consists of three wireless body-worn inertial motion sensors, each containing a triaxial accelerometer and gyroscope. Two sensors were placed on the left and right shank, 4 cm superior and anterior to the malleolus, the third was placed on the lumbar trunk at the L5 spinous process. The sensors transmitted their data online to a wireless receiving station plugged into a portable personal computer and were analysed offline using the IWALK plugin for the Mobility Lab software package (APDM, Portland, USA). Heel contact for each foot was defined as the peak negative shank angular velocity following mid-swing (Aminian et al., 2002) recorded by the shank gyroscopes (range ± 2000 °/s, sample rate 128 Hz). The time between successive heel contacts with the ground of the same leg was recorded as the gait cycle. Stride time (s) was recorded as the mean combined gait cycle time for both legs. Trunk angular distance in both the AP and ML directions was integrated from the trunk and shank gyroscope data which underwent bias removal and processing in Mobility Lab.

4.3.3 Conditions

Participants walked under three different cognitive task conditions: walking only with no concurrent task (WALK), walking whilst performing a serial subtractions serial subtraction task (SERIAL7) and walking whilst performing a working memory task (2BACK). During the WALK condition, participants were asked to "walk normally" for two minutes. A white circle (4 cm in diameter) was projected against a black background, from a personal computer (Aspire 5742, Acer, New Taipei City, Taiwan) onto the wall mounted projection screen 350 cm from the treadmill by a ceiling mounted projector (Gt750 DLP, Optoma, Watford, UK). In order to ensure gaze was controlled across trials, participants were instructed to "walk normally whilst looking at the white circle" in all conditions. During the SERIAL7 serial subtraction task, participants were asked to subtract in sevens starting from a number between 591-595. Participants were asked to accurately count aloud as many numbers as possible for 120 s. Reponses were recorded using the Audio Memos software package (version 3.6, Imesart, Luxembourg) on a tablet computer (iPad, Apple, Cupertino, USA) and analysed off-line. During the 2BACK working memory task, a series of 50 pseudo randomised letters (A-J), were projected consecutively on to the wall mounted screen. Each white letter was presented against a black background for 500 ms, with an inter stimulus interval of 1900 ms. If the letter on the screen matched the letter displayed two stimuli previously (i.e. two back) then participants pressed a button on a handheld infrared mouse (SP400, Duronic, London, UK). There were a possible 10 correct responses (20% of total stimuli) in each set of 50 letters. The 2BACK task was programmed using DMDX software package (University of Arizona, Arizona, USA). For both tasks, the error ratio was calculated using methods described in the general methods (Equation 4 and 5 for 2-back and serial subtraction respectively).

Differences in difficulty between walking speeds and each condition were assessed in a sub-set of the participants (n = 10) using the Borg CR10 scale (Borg, 1998), a 10 point scale which asks participants to rate the difficulty of the task on a scale from 0-10

4.3.4 Procedure

Initially, each participant's preferred walking speed was determined by repeating the following assessment four times and calculating the mean average threshold for identification: starting at 2.0 km.h^{-1}, participants walked on the treadmill whilst speed was increased in 0.1 km.h^{-1} increments until the participant reported that the speed equalled their preferred walking speed. Treadmill speed was then increased to 6.5 km.h^{-1} and lowered in 0.1 km.h^{-1} increments until the participant again identified their preferred speed. Subsequently, participants performed SERIAL7 and 2BACK whilst stood on a stationary motorised treadmill. These data were used as baseline measurements for cognitive task performance (stationary). Participants then walked on the treadmill for two, six-minute stages at either their preferred walking speed or at 25% of their preferred walking speed (slow walking speed) in a counter balanced order. Before each stage began, participants walked for 45 seconds to adjust to the treadmill speed. During each six-minute stage, participants performed WALK, SERIAL7 and 2BACK for two minutes each, in a counterbalanced order. In both dual-task conditions, participants were not given any instructions on whether to prioritise cognitive task or gait performance. Participants rested for 30 seconds between the different waking speed conditions.

4.3.5 Data analysis

Two-way (speed x task) repeated measures analysis of variance (ANOVA) were used separately to determine the effect of walking speed and cognitive task on the following measures; STV, AP and ML trunk RoM. Where a significant effect was found, Bonferroni corrected pairwise comparisons were used to determine the location of the effect. Effect sizes for main effects and interactions are presented as partial eta squared (*ηp*) and for pairwise comparisons as Cohen's *d* (*d*). Logarithmic transformations were used to normalise non-gaussian data. STV was calculated as the coefficient of variation (%) of stride time. Trunk RoM was calculated as the trunk angular distance (degrees) covered (in the AP and ML directions) per gait cycle. For both SERIAL7 and 2BACK, the number of correct answers and errors were recorded when stationary and when walking at preferred and slow walking speeds.

Due to cognitive task and perceived difficulty data being non-parametric, differences in task performance and perceived task difficulty between each walking speed (stationary, preferred and slow) were examined using Friedman's ANOVA for each task. Significant effects were followed up with Bonferroni corrected Wilcoxon signed rank tests. Effect sizes for significant effects are presented as *r*. A *p* value of < 0.05 was considered significant. Data were analysed using the SPSS software package (Version 18, IBM corp, Armonk, NY, USA).

4.4 Results

4.4.1 Gait analysis

Participants' mean preferred walking speed was 1.33 ± 0.21 $m.s^{-1}$. Mean strides per trial and stride time for both walking speeds across all task conditions are shown in Table 2.

Table 2. Mean ± SD number of strides and stride time (s) across the preferred and slow walking speeds for all task conditions

	Walking speed					
	Preferred			Slow		
	Task					
	WALK	SERIAL7	2BACK	WALK	SERIAL7	2BACK
Strides	108.7±8.0	109.3±7.7	111.1±8.6	53.8±7.9	54.7±8.4	56.6±7.1
Stride Time(s)	1.05±0.08	1.07±0.08	1.07±0.08	2.16±0.29	2.12±0.32	2.09±0.25

4.4.2 Effect of Cognitive Task Type on Gait Variability and Trunk RoM

Mean STV and trunk RoM during single and dual-task gait are displayed in table 3. ANOVA revealed a significant effect of cognitive task on STV ($F_{(2,42)}$=8.3, p=0.001, ηp=0.283). Bonferroni corrected follow up analysis revealed that STV was higher during WALK than 2BACK (p=0.02, d=0.37) and SERIAL7 (p=0.01, d=0.40) but there was no difference in STV between 2BACK and SERIAL7 (p=1.0, d=0.22, Figure 16).

There was an effect of cognitive task on AP trunk RoM ($F_{(2,42)}$=7.2 p=0.02, ηp=0.256) where AP trunk Rom was higher SERIAL7 than during WALK (p=0.023, d=0.18) and 2BACK (p=0.022, d=0.20). There was no effect of cognitive task on ML trunk RoM ($F_{(2,42)}$=0.2 p=0.791, ηp=0.011).

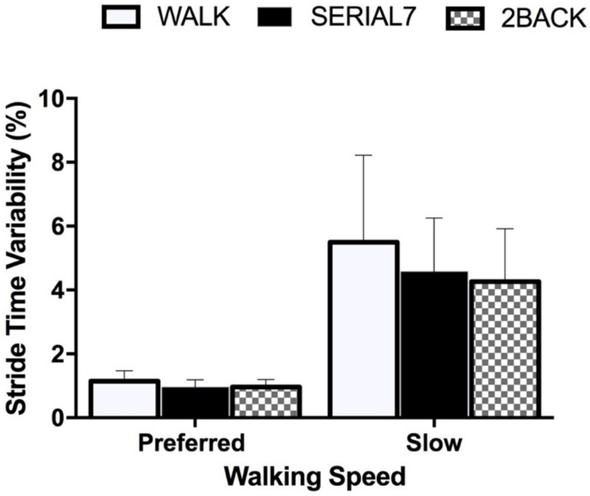

Figure 16. Mean stride time variability. After logarithmic transformation, STV was significantly lower during both SERIAL7 and 2BACK compared to WALK at both speeds, and was significantly higher at the slow walking speed compared to the preferred walking speed. Error bars represent 1SD.

4.4.3 Effect of Walking Speed on Gait Variability and Trunk RoM

ANOVA revealed a significant effect of walking speed on STV ($F_{(1,21)}$=653.4, p<0.001, ηp=0.969) where STV was higher at the slow walking speed than at preferred walking speed. There was no significant interaction between walking speed and cognitive task type on STV ($F_{(2,42)}$=1.0, p=0.388, ηp=0.044).

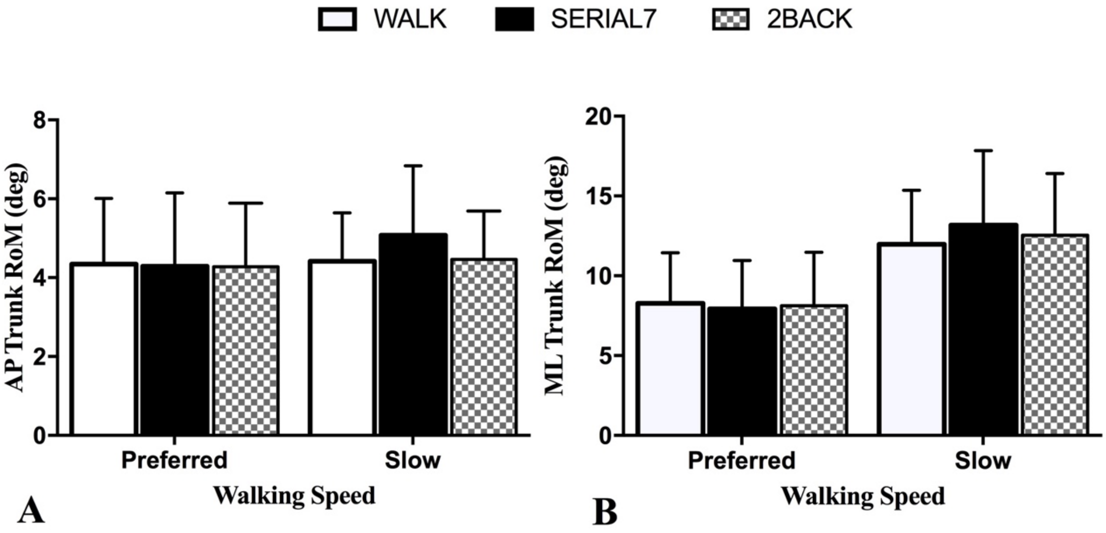

Figure 17. Mean AP (graph A) and ML (graph B) trunk RoM. After logarithmic transformation AP trunk RoM was significantly higher during SERIAL7 than during WALK and 2BACK at the slow walking speed only. ML trunk RoM was significantly higher at the slow walking speed than at the preferred walking speed. Error bars represent 1SD.

There was no effect of walking speed on AP trunk RoM ($F_{(1,21)}$=1.0, p=0.324, ηp=0.046) However there was a speed by task interaction ($F_{(2,42)}$=8.4 p=0.01, ηp=0.285, see Figure 17A) where AP trunk RoM was higher during SERIAL7 than WALK (p=0.01, d=0.69) and 2BACK (p = 0.01, d=0.73) at the slow walking speed only. There was an effect of walking speed on ML trunk RoM ($F_{(1,21)}$=27.9, p<0.001, ηp=0.570) where trunk RoM was higher at the slow walking speed than at the preferred walking speed (Figure 17B). There was also an interaction between walking speed and cognitive task type on ML trunk RoM ($F_{(2,42)}$=5.6, p=0.007, ηp=0.211). However, Bonferroni corrected pairwise comparison revealed that there were no statistically significant differences in ML trunk RoM between SERIAL7, 2BACK and WALK at either speed (all p>0.05).

Table 3. Mean ±SD Stride time variability and trunk RoM across the preferred and slow walking speeds for all task conditions

	Walking Speed					
	Preferred			Slow		
	Task					
	WALK	SERIAL7	2BACK	WALK	SERIAL7	2BACK
STV (%)	1.1±0.4	0.96±0.2	0.92±0.3	5.3±2.9	4.4±1.9	4.1±1.9
AP trunk Rom (deg)	4.3±1.7	4.3±1.9	4.3±1.6	4.4±1.2	5.1±1.8	4.5±1.2
ML trunk Rom (deg)	6.2±3.2	6.1±3.0	6.2±3.3	8.1±3.4	9.0±4.7	8.4±3.9

4.4.4 Cognitive Task Performance and Perceived Task Difficulty

Mean cognitive task performance data are presented in Table 4. The Friedman's ANOVA revealed no significant effect of walking condition on SERIAL7 task performance ($X^2_{(2)} = 1.2$ p=0.53). There was also no difference between the effect of each walking conditions on the 2BACK test performance ($X^2_{(2)}$=4.6, p=0.10).

Table 4. Median ± IQR number of correct responses and errors in both the SERIAL7 and 2BACK tasks across the three walking conditions (stationary, preferred walking speed and slow walking speed)

Task	Measure	Walking speed		
		Stationary	Preferred	Slow
Serial 7	Correct responses	27 ± 15	32 ± 17	32 ± 16
	Errors	2 ± 4	3 ± 3	1 ± 3
2BACK	Correct responses	9 ± 2	9 ± 3	9 ± 2
	Errors	3 ± 3	3 ± 4	2 ± 3

There was a significant effect of walking speed on SERIAL7 perceived task difficulty ($X^2_{(2)}$=9.9, p=0.007). Perceived difficulty was higher during walking at the slow walking speed compared to walking at preferred walking speed (T=41.0, r=0.52). There was no effect of walking condition on perceived difficulty of the 2BACK task ($X^2_{(2)}$=0.64, p=0.73).

4.5 Discussion

In the present study the effects of cognitive task type and walking speed on dual-task gait were examined. Whilst both the serial subtraction and N-back tasks reduced STV, there was no difference in the size of this reduction between the tasks. As expected, STV was higher at the slow walking speed and there was a significant interaction between walking speed and cognitive task on trunk RoM, where the serial subtraction task increased AP trunk RoM when walking at the slow speed only. These findings suggest that the control of gait is shared by cognitive systems sub-serving both serial subtraction and N-Back working memory tasks in healthy adults. These results also indicate that trunk RoM is affected by both the walking speed and cognitive task type used during dual-task gait.

4.5.1 Effect of Cognitive Task Type on Dual-Task Gait

In the present study, both cognitive tasks reduced STV of gait and, in contrast to our predictions, where not different from each other. Whilst performance of a concurrent serial subtraction task during gait has previously been shown to increase STV (Beauchet et al., 2005b), N-Back working memory tasks have been reported to reduce STV (Lövdén et al., 2008; Schaefer et al., 2010). This has led some to suggest that the cognitive processes required to perform the N-back test are not shared with the control of gait (Beurskens and Bock, 2012). The present results do not support this suggestion, because both the working memory and serial subtraction tasks reduced STV. Lövdén et al., (2008) suggested that reduced STV during dual-task gait indicates the adoption of a smoother, automatic gait pattern, which may occur because the performance of a concurrent dual-task redirects attention away from gait to the cognitive task. The present findings support the suggestion that performance of a cognitive task, regardless of task type, may redirect high-level cognitive processes away from gait toward the cognitive task.

Previous researchers have reported that STV was negatively related to performance in tests of executive function, and suggested this indicated that the maintenance of steady walking requires input from cognitive and attentional processes, perhaps to allow the walker to adapt to perturbations (Hausdorff et al., 2005; Beauchet et al., 2012). The present findings support this suggestion, and add to the growing body of evidence which links the control of gait to high level cognitive processes and attention. However, the reduction in STV in the present study are in contrast to a number of previous studies which have reported increased STV during dual-task gait (Kavanagh, 2009; Asai et al., 2013; Beauchet et al., 2009c, 2005b). Whilst those previous studies utilised over-ground walking protocols, the present study utilised a treadmill walking protocol. A reduction in STV during dual-task gait was also reported in two other studies that used treadmill walking (Lövdén et al., 2008; Schaefer et al., 2010). Therefore, although speculative, it is possible that the disparity between the results of this study and those of previous studies which reported increased in STV during dual-task gait may be explained by the differences in walking modality. Treadmill walking leads to locomotion without the individual moving through the environment, which may reduce the need to assess the walk-ability of the environment and encourage participants to focus attention away from walking performance, Indeed, Simoni et al., (2013) have reported that over-ground and treadmill walking modalities differently influence STV and cognitive task performance during dual-task gait. The biomechanical differences between over-ground and treadmill walking, which include reduced knee and hip range of motion, reduced peak breaking ground reaction force and differences in muscle activation patterns, have been well described (Riley et al., 2007; Lee and Hidler, 2008). However, less is known about the possible effects of each walking protocol on cognitive load and this maybe a possible topic for future research.

4.5.2 Effect of Walking Speed on Dual-Task Gait

In the present study, walking at a slow walking speed increased STV, as reported previously (Jordan et al., 2007; Beauchet et al., 2009c). Beauchet et al. (2009) suggested that changes to STV when walking at slow walking speeds may be caused by either increased cognitive involvement or other, biomechanical, factors. If the increased STV during slow walking was due to a greater demand on cognitive processes during gait, then one would expect the effects of the dual-tasks on gait to be different across the walking speeds. Because the effect of both cognitive tasks on STV was not different at either walking speed, our findings suggest that factors other than an increased demand on cognitive processes lead to increased STV during slow walking, such as changes to the walkers biomechanics (Dubost et al., 2006).

There was a significant interaction effect between walking speed and task type on AP trunk RoM, where AP trunk RoM was higher during performance of SERIAL7 than during either 2BACK or WALK at the slow walking speed. Previous dual-task gait research has been based on the assumption that changes to gait performance during dual-task gait indicate competition between the cognitive and gait tasks for shared high-level cortical processes (Yogev-Seligmann et al., 2008). One interpretation of these findings is that trunk stabilisation during slow walking may be dependent on high-level processes shared with the serial subtraction task. Whilst the N-back test examines working memory performance, the serial subtraction task is suggested to test attention and concentration (Ganguli et al., 1990) and thus the present results suggest that the control of trunk stabilisation during slow walking also requires attention.

4.5.3 Effect of Task Difficulty on Dual-Task Gait

The difficulty of the dual task is also suggested to influence dual-task gait performance (Brown et al., 2005; Kelly et al., 2013). In the present study walking speed influenced perceived task difficulty: participants found serial subtraction task performance during dual-task gait at the slow walking speed more difficult than during the preferred walking speed, which may have resulted in the different effects of the tasks in trunk RoM at the slow speed. The perceived difficulty during dual-task gait at the slow walking was still only moderately difficult (Borg, 1998). It is possible that the use of a treadmill to constrain the walking speed did not present a challenging enough walking condition to moderate the effect of the dual-task on STV.

The response modality of our cognitive tasks were different. Armieri, and colleagues (2009) reported that articulated responses in a digit span working memory task increased the dual-task cost on gait compared to silent rehearsal of the answers. Here, the serial subtraction task required responses to be articulated, whilst the N-back task required button presses in response to relevant stimuli. These differences may thus have resulted in the tasks engaging different processes and be responsible for the differing effects on trunk RoM. We consider this explanation unlikely because one would expect these differences in trunk RoM to be present at both treadmill speeds, however, they were only seen at the slow speed. Previously, Huxhold et al., (2006) reported that it is the relative task difficulty and level of attention paid to the task, rather than the nature of the response, that effects postural control during dual-task performance and the results of the present study support this suggestion.

4.6. Conclusion

In conclusion, here stride time variability was reduced during dual task-gait, but neither walking speed nor cognitive task type mediated this effect. This result indicates that during dual-task gait, the performance of a concurrent cognitive task may reduce the input from high-level cognitive processes for the control of gait, regardless of the nature of either the cognitive task or walking speed. Trunk range of motion increased during performance of a serial subtraction task, but not during an N-back working memory task, at the slow walking speed only suggesting both walking speed and cognitive task type may effect trunk RoM during dual-task gait. Because cognitive task type and walking speed changes some aspects of dual-task gait, researchers should consider the way in which these variables effect gait when designing dual-task gait studies and when interpreting the effect of the dual-task used on gait.

5. Effect of Transcranial Direct Current Stimulation on Task Processing and Prioritisation During Dual-Task Gait

5.1 Abstract

The relationship between cognition and gait is often explored using a dual-task gait paradigm, which represents the ability to divide cognitive resources during walking. Recent evidence has suggested that prefrontal cortex is involved in the allocation of cognitive resources during dual-task gait, though its precise role is unclear. Here, we used anodal and cathodal tDCS to probe the role of prefrontal cortex in the control of STV, trunk RoM and cognitive task performance during dual-task gait. As task difficulty has been shown to mediate the dual-task cost, we also manipulated walking speed to see if the effects of tDCS on dual-task gait were influenced by walking difficulty. Ten adults performed a serial subtraction task when walking at either preferred walking speed or at 25% of preferred walking speed, before and after receiving tDCS of the left prefrontal cortex. Anodal tDCS reduced STV and the dual-task cost on STV, and improved cognitive task performance. Cathodal tDCS increased STV and appeared to increase the dual-task cost on STV, but did not affect cognitive task performance. There was no effect of tDCS on trunk RoM and the effects of tDCS were not mediated by walking speed. The effect of dual-task gait on stride time variability and cognitive task performance was altered by the application of tDCS, and these effects were polarity dependent. These results highlight the role of prefrontal cortex in biasing task performance during dual-task gait and indicate that tDCS may be a useful tool for examining the role of the cortex in the control of dual-task gait.

5.2 Introduction

A growing body of evidence supports a link between gait and cognition. Rather than being an automated task requiring little top down control, the control of gait involves high-level cognitive processes (Woollacott and Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). The relationship between cognition and gait performance is typically explored a using dual-task gait paradigm, which probes an individual’s capacity to divide and allocate cognitive resources during walking

(Yogev-Seligmann et al., 2008; Al-Yahya et al., 2011). During dual-task gait, participants simultaneously perform a cognitively demanding task whilst walking. Changes in walking performance, cognitive task performance, or both, represent competition for shared central resources which are limited in capacity (Woollacott and Shumway-Cook, 2002; Huang and Mercer, 2001). Both the variability of stride time (STV), which is an indicator of gait automaticity and stability, and trunk motion, which is an indicator of postural control and stability, are frequently used to interpret the role of cognition in the control of gait (IJmker and Lamoth, 2012; Hausdorff, 2001). Changes in both STV and trunk motion are used to assess fall risk and gait rehabilitation interventions in older and cognitively impaired adults (de Hoon et al., 2003; Montero-Odasso et al., 2012).

The left prefrontal cortex is has been implicated in the allocation of cognitive resources between two simultaneously performed tasks (Collette et al., 2005) and recent evidence from studies using functional near-infrared spectroscopy has revealed that there is increased prefrontal cortex activation during dual-task gait (Holtzer et al., 2011; Doi et al., 2013). There is a growing body of research indicating that tDCS of prefrontal cortex influences cognitive function (Kuo and Nitsche, 2012). Only one study has used tDCS as an intervention in dual-task gait: Zhou and colleagues (2014) reported that prefrontal anodal tDCS with a current intensity of 1.5 mA reduced the dual-task cost on gait speed and trunk motion. Anodal tDCS was thought to increase the availability of cognitive resources for task performance. However, there was no effect of prefrontal tDCS on STV or cognitive task performance. As a result, the precise role of prefrontal cortex in the control of dual-task gait is not clear. During the performance of two simultaneous tasks, prefrontal cortex is suggested to exert top-down control on task performance by biasing cognitive processing (Miller and Cohen, 2001). Therefore, it is possible that, rather than increasing cognitive capacity, prefrontal anodal tDCS increased the bias and allocation of cognitive resources to one aspect of dual-task gait performance, gait speed. If prefrontal cortex is involved in the bias and prioritisation of aspects of task performance during dual-task gait, then prefrontal cathodal tDCS, which reduces cortical activity, might be expected to interfere with ongoing bias signals from prefrontal cortex, resulting in performance decrements in one or both tasks (Johnson et al., 2007; Vines et al., 2006). Examining the effects of both prefrontal anodal and cathodal tDCS may thus help identify the role of prefrontal cortex in the control of dual-task gait.

The effect of tDCS on STV and cognitive task performance may also be influenced by task difficulty. Dual-task gait performance is mediated by the relative difficulty of both the walking and cognitive task (Chapter 4), because more difficult motor or cognitive tasks reduce the availability of shared high-level cognitive sources (Huang & Mercer 2001). STV increases during more difficult walking, indicating an increased contribution from high-level resources (Kelly et al., 2010; Hausdorff, 2005). In the study by Zhou et al (2014), participants walked at their preferred walking speed whilst performing serial subtractions. As tDCS is suggested to influence the allocation of cognitive resources during dual-task performance (Zhou et al., 2014) then the walking speed (i.e. the difficulty of the walking task) may mediate the effect of tDCS on dual-task gait.

The primary aim of this study was to examine the role of prefrontal cortex in the control of dual-task gait using anodal and cathodal tDCS. We hypothesised that prefrontal anodal tDCS would amplify the bias of one task over the other, whilst cathodal tDCS would interfere with usual task bias during dual-task gait. We also hypothesised that the effects of tDCS would be mediated by walking speed.

5.3 Methods

5.3.1 Participants

Ten right handed males (mean + SD age: 23.0 + 3.2 years) volunteered to participate in the study. Handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971). Informed consent was obtained from all participants included in the study. Medical contra-indications to tDCS were screened using self-completed health questionnaires. Exclusion criteria for enrolment included epilepsy, surgically implanted materials in the head or neck, known allergies to preparation materials, a history of psychiatric disease or previous neurosurgical procedures. All procedures were conducted in accordance with the declaration of Helsinki and were approved by the local University ethical committee.

5.3.2 Gait analysis

Temporal gait variables and trunk motion were recorded using a portable gait analysis system which consisted of three body worn sensors, each containing a triaxial accelerometer and gyroscope (OPAL, APDM, Portland, USA). Two sensors were placed on the shank of each leg, anterior and 4cm superior to the malleous process. The third sensor was placed on the lumbar spine, at section L5. The method by which spatio-temporal gait parameters (STV and trunk RoM) are derived from angular accelerations of each shank are described in detail elsewhere (see Salarian et al. 2004 and General methods).

5.3.3 Cognitive Task

Starting from a number between 590-600, participants were required to verbally subtract in sevens for 120s. The starting number for each trial was chosen by using a pseudo-randomisation function in Microsoft Excel (Version 2013, Microsoft Corporation, Redmond, USA). The number of correct responses and errors were recorded using a portable digital dictaphone (UX200, Sony, Tokyo, Japan) and analysed off-line. The ratio of errors to correct answers (error ratio) was then calculated (see Equation 5 in general methods).

5.3.4 Transcranial Direct Current Stimulation

Transcranial stimulation was delivered via a programmable battery driven stimulator (HDCkit, Newronika, Milan, Italy). Participants received anodal, cathodal or sham tDCS in a randomised order. The stimulator was programmed by a technical member of staff not involved in the study and both participant and experimenter were blind to the stimulation condition. Both active and reference rubber electrodes were placed in saline soaked sponges. The active electrode was 35 cm^2 in size and was placed over the left prefrontal cortex at F3 using the 10-20 EEG system. The reference electrode was 72 cm^2 in size and was placed over the contralateral supra-orbital region. We chose to use a larger reference electrode to reduce current density and stimulation efficacy at this site (Nitsche et al., 2008). The applied current was 1.5 mA, giving a current density of 0.043 mA/cm^2 under the active electrode and 0.021 mA/cm^2 under the reference electrode. Current was ramped up for 15 s in all conditions. For the active (anodal and cathodal) conditions, stimulation was applied for 15 minutes. For the sham condition, current was switched off after 30 s (Gandiga et al., 2006).

5.3.5 Procedure

Initially, following familiarisation with experimental procedures, participants' preferred walking speed was determined. Starting at 2.0 km.h^{-1}, participants walked on a motorised treadmill (CLST, Life Fitness, Cambridge, UK). Participants were blinded to their walking speed. Walking speed was increased in 0.1 km.h^{-1} increments until the participant indicated that they were walking at their preferred speed. Walking speed was then increased to 6.5 km.h^{-1} and reduced in 0.1 km.h^{-1} increments until participants indicated that they were walking at preferred walking speed. This process was repeated and the mean of the four identified speeds was recorded as each individual's preferred walking speed.

Following familiarisation, each participant then participated in three testing sessions separated by at least 48 hours. The protocol during each session was as follows: initially participants performed the serial subtraction task whilst standing facing a fixation point 2 m in front of the treadmill. This served as the single task condition for the cognitive task. Subsequently, participants walked for 240 s at both their preferred walking speed and a speed equal to 25% of preferred walking speed, in a counterbalanced order. Participants rested for 30 s between each walking speed change, and walked for 30 s at the new speed before data collection began. During each four-minute stage, participants walked for 120 s with no additional task (single task) and for 120 s whilst performing the serial subtraction task (dual-task), also in a counterbalanced order. After both walking stages were completed, the participants' received tDCS whilst seated. Participants were asked to sit in silence without performing any other task during the stimulation. After stimulation cessation, the walking protocol was immediately repeated.

5.3.5 Data Analysis

All data are reported mean + SD. We examined the effect of tDCS and walking speed on dual-task gait and on the dual-task cost on STV, trunk RoM and error ratio. The dual-task cost, a measure of change from single to dual-task conditions (Kelly et al., 2010), was calculated for STV and trunk RoM (see Equation 6, General

Methods). Because an error ratio of zero is possible, the dual-task cost on cognitive task performance was calculated (see Equation 7, General Methods)

The effects of stimulation and walking speed on dual-task gait were examined using a three way repeated measure ANOVA (stimulation condition [anodal, cathodal and sham] x walking speed [preferred, slow] x time [pre and post stimulation]). Significant effects were followed up using Bonferroni-corrected pairwise comparisons. Non-Gaussian data were normalised using logarithmic and square root transformations (Tabachnick and Fidell, 2007). If data remained non-parametric after transformation, the effects of stimulation were analysed at each speed using a two way Freidman's ANOVA with Bonferroni-corrected Wilcoxon signed rank tests follow up. Statistical significance was set at $p<0.05$. Partial eta squared (ηp) was used as a measure of effect size for main and interaction effect sizes and Cohen's d_{av} for within subjects repeated measures (d) was used for pairwise comparison effect sizes (Lakens, 2013).

5.4 Results

5.4.1 Gait Analysis

Participants' mean preferred walking speed was 1.2 + 0.07 m.s^{-1}. Mean + SD number of strides and stride time (s) for each speed (across all three stimulation conditions and times) are presented in Table 5.

Table 5. Number of strides and stride time (s) for each speed averaged across all three

	Preferred	Preferred+ Serial 7s	Slow	Slow+ Serial 7s
Strides	103.5±5.7	103.1±5.7	51.3±8.2	51.6±7.3
Stride time (s)	1.1±0.1	1.1±0.1	2.3±0.3	2.3±0.3

5.4.2 Effect of tDCS on Stride Time Variability

Table 6 shows the mean STV and trunk Rom during dual-task gait, and the mean dual-task cost on STV and trunk RoM. For STV during dual-task gait, after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}=0.5$, $p=0.611$, $\eta p=0.053$) or time (pre-post) ($F_{(1,9)}<0.1$, $p=0.990$, $\eta p<0.001$).

There was an effect of walking speed on STV, where STV was higher at the slow walking speed ($F_{(1,9)}=505.6$, $p<0.001$, $\eta p=0.983$). There was a significant interaction between stimulation condition and time ($F_{(2,18)}=5.0$, $p=0.019$, $\eta p=0.355$). Bonferroni corrected pairwise comparisons revealed that STV decreased after anodal tDCS ($p=0.011$, $d=0.1$) and increased after cathodal tDCS ($p=0.029$, $d=0.2$). There was no difference in STV after sham tDCS ($p=0.535$, $d=0.1$). There was no interaction between stimulation condition, walking speed and time ($F_{(2,18)}=1.2$, $p=0.330$, $\eta p=0.116$).

For the dual-task cost on STV, after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}=2.5$, $p=0.112$, $\eta p=0.216$), time (pre-post) ($F_{(1,9)}=1.4$, $p=0.394$, $\eta p<0.001$) or of walking speed ($F_{(1,9)}=0.5$, $p=0.494$, $\eta p=0.053$). There was a significant interaction between stimulation condition and time ($F_{(2,18)}=3.8$, $p=0.041$, $\eta p=0.299$, Figure 18). The dual-task cost on STV was lower after anodal stimulation ($p=0.002$, $d=0.6$) and there was a trend for the dual task cost on STV to be higher after cathodal tDCS ($p=0.063$, $d=0.6$). There was no difference in the dual-task cost on STV after sham stimulation ($p=0.765$, $d=0.1$). Again, there was no interaction between stimulation condition, walking speed and time ($F_{(2,18)}=0.6$, $p=0.578$, $\eta p=0.059$).

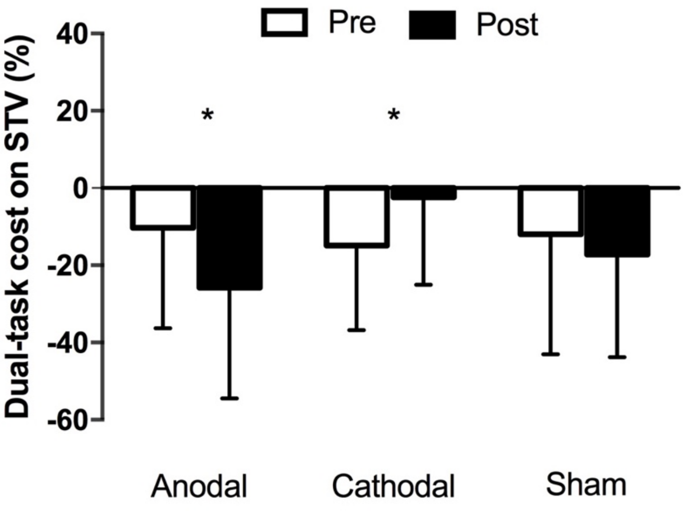

Figure 18. Mean dual-task cost on STV pre and post tDCS, across both speeds. Error bars represent 1 SD. * Signifies a difference pre to post stimulation.

For ML trunk RoM after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}=0.6$, $p=0.578$, $\eta p=0.059$) or time (pre-post) ($F_{(1,9)}<0.1$, $p=0.976$, $\eta p<0.001$). There was an effect of walking speed on ML trunk RoM where trunk RoM was lower at the slow walking speed ($F_{(1,9)}=12.4$, $p=0.006$, $\eta p=0.983$). There was no interaction between stimulation condition and time ($F_{(2,18)}=1.6$, $p=0.238$, $\eta p=0.147$) and no three-way interaction between stimulation condition, time and walking speed ($F_{(2,18)}=1.6$, $p=0.225$, $\eta p=0.153$). For AP trunk RoM after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}<0.1$, $p=0.979$, $\eta p=0.002$), time (pre-post) ($F_{(1,9)}=2.9$, $p=0.121$, $\eta p=0.246$) or walking speed ($F_{(1,9)}=4.7$, $p=0.059$, $\eta p=0.342$). There was also no interaction between stimulation and time ($F_{(2,18)}=0.6$, $p=0.577$, $\eta p=0.059$) or between stimulation, time and walking speed ($F_{(2,18)}=0.1$, $p=0.949$, $\eta p=0.006$).

Table 6. Stride time variability (%), ML trunk Rom (deg) and AP trunk RoM (deg) across stimulation conditions for preferred and slow walking speeds

		Anodal		Cathodal		Sham	
	Speed	Pre	Post	Pre	Post	Pre	Post
STV (%)	Pref	1.2±0.3	1.0±0.2	1.1±0.3	1.24±0.4	1.1±0.4	1.1±0.2
	Slow	5.5±1.2	5.3±1.0	5.0±1.43	5.9±1.7	5.7±2.5	5.5±1.9
DTC STV (%)	Pref	-15.2±16.6	-31.9±24.1	-12.7±21.2	-8.3±16.3	-11.5±32.7	-16.1±22.9
	Slow	-5.4±33.2	-19.8±32.7	-17.1±23.4	3.5±27.2	-12.4±31.0	-18.3±31.1
ML trunk RoM (deg)	Pref	8.4±3.1	8.7±3.2	8.1±2.6	8.1±2.2	8.2±3.2	8.5±3.5
	Slow	4.4±1.6	4.7±1.3	4.6±1.1	4.7±1.5	6.3±3.1	5.6±2.3
DTC ML RoM (%)	Pref	-3.4±11.4	-1.0±8.0	0.8±9.2	-2.1±8.3	-1.4±4.5	4.5±11.3
	Slow	-0.3±9.6	2.2±16.9	0.9±27.3	10.8±30.4	3.5±21.1	6.5±13.6
AP trunk RoM (deg)	Pref	4.1±2.0	3.8±1.4	3.9±1.4	3.9±1.8	4.0±1.6	4.1±1.4
	Slow	4.5±0.8	4.8±0.8	4.6±1.0	5.0±1.5	4.4±1.1	4.9±1.4
DTC AP RoM (%)	Pref	1.0±9.6	-1.8±4.8	-2.4±2.6	-4.4±3.8	-3.3±6.3	2.3±8.7
	Slow	19.2±27.0	6.7±15.8	3.1±11.0	6.0±17.6	-4.1±16.7	12.3±10.0

DTC; Dual-task cost, Pref; preferred walking speed, Slow; slow walking speed

At the preferred walking speed, there was no interaction between stimulation and time on the dual-task cost on ML trunk RoM ($X^2_{(5)}$=1.4, p=0.925) or AP trunk RoM ($X^2_{(5)}$=8.4, p=0.136). At the slow walking speed, there was no significant interaction between stimulation condition and time on the dual-task cost on ML trunk RoM ($X^2_{(5)}$=4.8, p=0.444). There was a significant interaction between stimulation condition and time on the dual-task cost on AP trunk RoM ($X^2_{(5)}$=11.4, p=0.042) however Bonferroni corrected follow up revealed no statistically significant differences in AP trunk RoM following stimulation (all p>0.05).

5.4.3 Effect of tDCS on Cognitive Task Performance

Table 7 dislpays the mean ± SD error ratio and dual-task cost on the error ratio. For error ratio during dual-task gait, after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}$=1.8, p=0.202, ηp=0.163, time (pre-post) ($F_{(1,9)}$=2.0, p=0.194, ηp=0.180) or walking speed ($F_{(1,9)}$=2.3, p=0.162, ηp=0.205). There was an interaction between stimulation condition and time ($F_{(2,18)}$=3.9, p=0.039, ηp=0.302). Error ratio was lower after anodal tDCS (p=0.004, d=1.1). There was no difference in error ratio after cathodal tDCS (p=0.925, d<0.1) or sham tDCS (p=0.324, d=0.4). There was no interaction between stimulation condition, time and walking speed ($F_{(2,18)}$=0.9, p=0.433, ηp=0.089).

Table 7. Error ratio (%), and the dual-task cost on error ratio (%) across stimulation conditions for preferred and slow walking speeds

		Anodal		Cathodal		Sham	
	Speed	Pre	Post	Pre	Post	Pre	Post
Error ratio (%)	Pref	5.37±4.23	1.30±1.69	4.18±5.18	4.05±4.01	1.63±1.62	3.14±2.65
	Slow	3.48±4.47	1.12±1.21	3.24±2.79	3.60±4.54	1.57±3.06	2.23±3.51
DTC (%)	Pref	1.28±3.96	-2.79±3.09	0.53±4.13	0.40±3.81	-2.21±5.63	-0.70±4.96
	Slow	-0.61±3.25	-2.97±3.09	-0.41±2.14	-0.05±4.70	-2.28±5.85	-1.62±3.69

DTC: dual-task cost, Pref: preferred walking speed, Slow; slow walking speed

For the dual-task cost on error ratio, after logarithmic transformation there was no main effect for stimulation condition ($F_{(2,18)}$=1.1, p=0.365, ηp=0.106, time (pre-post) ($F_{(1,9)}$=2,8 p=0.128, ηp=0.238) or walking speed ($F_{(1,9)}$=1.9, p=0.197, ηp=0.177).

There was an interaction between stimulation condition and time ($F_{(2,18)}$=4.1, p=0.034., ηp=0.313, Figure 19) where the dual-task cost on error ratio was lower after anodal stimulation (p=0.006, d=0.9). There was no difference in the dual-task cost on error ratio after cathodal tDCS (p=0.939, d<0.1) or sham tDCS (p=0.323, d=0.2). There was no interaction between stimulation condition, time and walking speed ($F_{(2,18)}$=0.7, p=0.523, ηp=0.069).

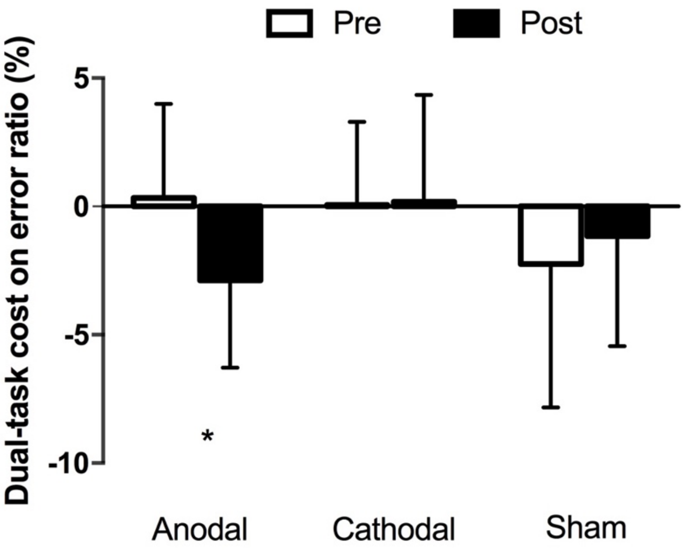

Figure 19. Mean dual-task cost on error ratio pre and post tDCS, across both speeds. Error bars represent 1 SD. * Signifies a difference pre to post stimulation.

5.5. Discussion

The primary aim of this study was to investigate the role of prefrontal cortex in the control of dual-task gait using transcranial direct current stimulation. Our secondary aim was to see if the effects of tDCS on dual-task gait were mediated by walking speed. As predicted, anodal tDCS decreased both STV and the dual-task cost on STV, and increased cognitive task performance. Conversely, cathodal tDCS increased STV and there was a trend for cathodal tDCS to increase the dual-task cost on STV. These findings support the suggestion that prefrontal cortex is involved in the bias and prioritisation of task performance during dual-task gait. In contrast to our predictions, the effects of tDCS on dual-task gait were not mediated by walking speed. These findings extend those of Zhou et al (2014) by showing that tDCS affects STV and cognitive task performance during dual-task gait on a treadmill and help to clarify the role of prefrontal cortex in the control of dual-task gait.

5.5.1 The Effect of tDCS on Dual-Task Gait

In the present study, anodal tDCS reduced STV and the dual-task cost on STV and improved cognitive task performance. Conversely, cathodal tDCS increased STV and appeared to increase the dual-task cost on STV. These results support the proposal that prefrontal cortex is involved in the bias and prioritisation of relevant task processes during dual-task gait. Prefrontal cortex activity increases when multiple cognitive processes compete for cognitive resources, suggesting that prefrontal cortex is involved in the prioritisation and filtering of relevant ongoing processes to achieve task relevant goals (Milham et al., 2003; Miller and Cohen, 2001). During dual-task gait on a treadmill, healthy adults may reduce their STV (Lövdén et al., 2008). A reduction in STV represents a reduction in the allocation of cognitive resources to the control of gait (Hausdorff, 2005), indicating that during dual-task gait on a treadmill participants prioritise the allocation of cognitive resources from gait to cognitive task performance (Lövdén et al., 2008). In the present study, prefrontal anodal tDCS appears to amplify this effect; further increasing the allocation of cognitive resources away from gait and toward cognitive task performance which leads to a reduced dual-task cost on STV and increased cognitive task performance. Conversely, prefrontal cathodal tDCS increased STV and there was a trend for cathodal tDCS to increase the dual-task cost on STV. It is tempting to interpret the effect of cathodal tDCS here as the opposite of the effect of anodal tDCS: that is, if a reduction in STV after anodal tDCS represents an increase in the allocation of cognitive resources away from gait, then an increase in STV may indicate that cathodal tDCS interferes with the allocation of cognitive resources away from gait toward cognitive task performance. Alternatively, as increased STV has been linked to age and disease related declines in cognitive and prefrontal cortex function (Allali et al., 2010; Beauchet et al., 2012; Hausdorff, 2005), here prefrontal cathodal tDCS may have reduced the availability of cognitive resources during dual-task gait by reducing prefrontal cortex activity, which led to an increase in STV during dual-task gait. Although the exact mechanism by which cathodal tDCS affects dual-task gait is unclear, the differing effects of both stimulation types indicate that prefrontal cortex is involved in the allocation of cognitive resources during dual-task gait.

In the present study, there was no effect of tDCS on trunk RoM. This may suggest that, whilst trunk RoM is affected by dual-task gait (Doi et al., 2011), prefrontal cortex is not involved in the control of trunk RoM during gait. Alternatively, it is possible these data here represent a ceiling effect in the control of trunk RoM in healthy adults. Asai et al (2013) reported age related differences in the control of trunk RoM during dual-task gait. It is possible that in older adults or clinical populations, there may be greater involvement from high level centres such as prefrontal cortex and tDCS of prefrontal cortex may effect trunk RoM in these groups. However, in contrast to the present findings, Zhou et al (2014) reported that anodal tDCS improved postural sway during a standing dual-task, suggesting that tDCS may affect trunk motion in healthy young adults under some circumstances.

Anodal tDCS is suggested to have the potential to be a useful therapeutic tool for gait rehabilitation (Zhou et al., 2014) and there is a large and growing body of evidence linking the application of anodal tDCS to improved cognitive functions (Kuo and Nitsche, 2012; Kadosh, 2013). In the present study, anodal tDCS (further) reduced STV during dual-task gait. Whilst high stride variability is often linked to falls (Hausdorff, 2001) very low stride variability may also increase fall risk (Brach et al., 2005). Therefore, increased allocation of cognitive resources from gait to cognitive task performance, which leads to a decreased STV, could be detrimental to gait stability and increase fall risk. Therefore, the results of the present study suggest anodal tDCS may not facilitate dual-task gait, as the exploitation of stride variability maybe required for optimum gait performance (Dingwell and Cusumano, 2010). Rather, the change in STV reported here only indicates that prefrontal cortex is involved in the control of dual-task gait. Whether these effects occur during over-ground walking is unclear however, as only Zhou et al (2014) have investigated the effect of anodal tDCS on over-ground dual-task gait, and found no effect on STV. The relative priority of each task (gait and cognitive) during dual-task gait may be influenced by the walking condition (Kelly et al., 2013) which may explain the disparity between the present results and those of Zhou et al (2014). In support of this suggestion, Simoni et al (2013) previously reported that older adults' dual-task gait and cognitive task performance were influenced by walking modality, and suggested that treadmill and over-ground walking may place different demands on cortical control centres. This disparity may have important implications for practitioners who use treadmills during rehabilitation in an effort to improve over-ground walking. Future studies should compare the involvement of prefrontal cortex in the control of dual-task gait in both walking modalities.

We chose not to record stimulation sensation or detection data after each trial, in order to reduce the possibly confounding effects of drawing participants' attention to the nature of the stimulation. However, it is possible that the effects reported here may have been influenced by the participants' perceptions during stimulation. We consider this unlikely however, as the current tDCS protocol is reported to be successful in blinding participants to the nature of the stimulation condition (Gandiga et al., 2006), even if there were reported differences in the sensations felt in both conditions (Russoa et al., 2013). Nonetheless, future studies using tDCS to examine brain function and cognition may want to record whether participants were accurately able to discriminate between active and sham stimulations (Russoa et al., 2013) in order to ensure blinding efficacy. Alternatively, a between-participant design could be used to avoid changes in awareness of stimulation sensation confounding subsequent stimulation conditions.

5.5.2 The Influence of Walking Speed on the Effect of tDCS on Dual-Task Gait

Our second aim was to examine whether the effect of tDCS on dual-task gait was mediated by walking task difficulty, which we increased by reducing walking speed. Task difficulty is a known mediator of the dual-task effect (Huang and Mercer, 2001) however, in contrast to our hypothesis, we found that the effects of tDCS on dual-task gait were not influenced by walking speed. One possible explanation for this finding is that increasing walking difficulty by decreasing walking speed does not influence prefrontal cortex activity, and the changes to gait during walking at a slow speed maybe dependent on factors other than cognitive function. Under these circumstances, the effects of tDCS of prefrontal cortex may not be mediated by walking speed.

5.6 Conclusion

In conclusion, here we report that anodal tDCS of the left prefrontal cortex increases the allocation of cognitive resources from gait toward cognitive task performance which occurs during dual-task gait on a treadmill, whereas cathodal tDCS may have interfered with the allocation of cognitive resources during dual-task gait performance. These results indicate that prefrontal cortex may be involved in the allocation and prioritisation of tasks during dual-task gait. These preliminary data also suggest that tDCS can be used to alter the ability of healthy adults to allocate cognitive resources during dual-task treadmill walking and may help to inform future research examining the effects of tDCS on fall risk and dual-task gait.

6. Effect of Prefrontal Cortex tDCS on Corticospinal Excitability and Cognitive Task performance

6.1 Abstract

The effect of prefrontal tDCS on corticospinal excitability and working memory performance was examined in 10 participants (2 female). On separate days, anodal, cathodal and sham tDCS were delivered in a randomised order. Before and after stimulation, corticospinal excitability was examined using TMS delivered to motor cortex representation of the right hand. Stimulations were delivered at rest and during a submaximal contraction. Working memory capacity was assessed with the 2-back working memory task. There was a reduction in corticospinal excitability following cathodal prefrontal tDCS, but no change after anodal or sham tDCS. There was no change in mean cognitive task performance following any stimulation condition and no relationship between change in corticospinal excitability and cognitive task performance following anodal tDCS. The present study failed to replicate the improvements in working memory performance following anodal tDCS that have been reported elsewhere. These results indicate the prefrontal tDCS may modulate the activity of the corticospinal motor system. The present study also highlights the high inter-individual variability in changes to cognitive task performance following tDCS.

6.2 Introduction

In Chapter 5, prefrontal anodal and cathodal tDCS appeared to influence dual-task gait performance. However, it is not clear what physiological mechanisms underpin these changes. Prefrontal cortex has been linked to task prioritisation during dual-task performance (Hobert et al., 2011) and thus alterations to prefrontal cortex function may result in altered prioritisation of either the cognitive or walking tasks (Wrightson et al. 2015, Chapter 5). Prefrontal tDCS may also influence performance through modulation of motor cortex activity. Inhibition of prefrontal cortex using repetitive TMS increases corticospinal excitability, suggesting an inhibitory influence on motor cortex by prefrontal cortex (Duque et al., 2012). Tunovic and colleagues (2014) propose that motor cortex and prefrontal cortex are part of a control network which mediates corticospinal excitability during task performance. It is possible that these effects may also occur after prefrontal tDCS, which influences neural network activity (Dayan et al., 2013). Indeed, Vaseghi et al. (2015) recently reported that cathodal prefrontal tDCS reduced corticospinal excitability. Currently, any changes to dual-task gait following tDCS are attributed to changes to cognitive network activity (Zhou et al., 2014). However, in order to interpret these effects correctly, it is important to fully understand the effects of prefrontal tDCS on corticospinal excitability.

Boros and colleagues (2008) reported no effect of anodal prefrontal tDCS on corticospinal excitability at rest. However, data from TMS studies indicate prefrontal inhibition of the corticospinal tract is dependent on task demands, specifically, when responding to visual cues (Hasan et al., 2013). Mandrick et al. (2013) reported an increase prefrontal cortex activation during sub maximal force production task, where participants are required to activate motor output. Thus, prefrontal activation, and presumably its influence on corticospinal excitability, may be dependent on whether an individual is at rest or performing an attention demanding task. For tDCS to be an effective tool to examine brain function, particularly cognitive-motor tasks such as dual-task gait, a fuller understanding of the system wide changes to activity that result from simulation is required. However, the effect of prefrontal tDCS on corticospinal excitability during cognitive and motor task execution is currently unknown.

Early tDCS reports described a polarity dependent effect of corticospinal excitability (Nitsche and Paulus, 2000, 2001). These were attributed to depolarisation and hyperpolarisation of neuronal cell membranes during anodal and cathodal tDCS, respectively (Stagg and Nitsche, 2011). However, recently a number of authors have reported considerable inter-individual variability in the physiological response to tDCS (Wiethoff et al., 2014; López-Alonso et al., 2015; Horvath et al., 2014b). Cognitive effects of tDCS appear to be equally as variable. Early studies reported a similar dichotomy between the polarities where anodal tDCS improved, and cathodal tDCS hindered, cognitive performance (Fregni et al., 2005; Boggio et al., 2006). However, more recent studies reveal contrasting effects, including facilitatory effects of cathodal tDCS (Weiss and Lavidor, 2012; Filmer et al., 2013; Jacobson et al., 2012). Although the cause of these differences is unclear, anatomical differences between participants, genetic variation, individual personality traits and differences in the ‘state’ of the neuronal populations being stimulated have all been proposed (Nieratschker et al., 2015; Learmonth et al., 2015; Li et al., 2015). Bortoletto et al. (2015) reported that behavioural effects of motor cortex tDCS were correlated with corticospinal excitability changes. If this were also true of prefrontal tDCS, examining the effects of tDCS on corticospinal excitability may be a useful measure to examine an individual’ responsiveness to stimulation, and help interpret inter-individual variability in tDCS responses. However, to date, there has been no examination of the relationship between the effects of prefrontal tDCS on corticospinal excitability and behaviour.

In order for tDCS to be an effective tool to examine brain function, it is important to understand the mechanisms which underpin prefrontal tDCS changes on behaviour. The primary aim was to examine the effects of both anodal and cathodal prefrontal tDCS on corticospinal excitability and cognitive task performance. Because prefrontal cortex is activated during a sub maximal force production task (Mandrick et al., 2013) we hypothesised that anodal prefrontal tDCS would increase and cathodal tDCS decrease corticospinal excitability during a sub maximal force production task. In accordance with previously reported effects, we hypothesised that prefrontal anodal tDCS would improve working memory performance (Zaehle et al., 2011). Because there may be a relationship between physiological and behavioural effects of tDCS (Bortoletto et al., 2015), we also examined the relationship between the effects of prefrontal tDCS on cognitive task performance and corticospinal excitability.

6.3 Method

6.3.1 Participants

Ten healthy adults (two females, mean ± SD age = 25.5 ± 3.4 years) were recruited from within the faculty and student body of the University of Brighton. Following institutional ethical approval, participants were given written and verbal details of the procedures and gave written informed consent. Participants were screened for medical contra-indications to transcranial stimulation using a medical questionnaire (Rossi et al., 2009), and were classified as right handed using the Edinburgh Handedness Inventory (Oldfield, 1971) .

6.3.4 Transcranial Magnetic Stimulation

Assessment of corticospinal excitability was performed using single pulse TMS, delivered using a Magstim^{200} stimulator which has a maximum output of 2.5 Tesla (Magstim Company, Whitland, UK) with a flat figure of eight coil (7 cm diameter) placed tangentially to the scalp and at an angle of 45° to the midline. Correct coil placement determined was using the following method: after marking the vertex, the "hotspot" for TMS was identified as the area of left motor cortex which when stimulated using a stimulator intensity of 60% of maximum, resulted in the greatest MEP measured by EMG in the contralateral FDI. All stimulations were delivered with the coil placed at this hotspot. Subsequently, the stimulator intensity which resulted in an EMG response of below 0.05mV in four of eight stimulations (resting motor threshold) was determined by decreasing stimulator intensity in 1% increments from 70% of maximum stimulator output. All subsequent TMS were delivered at 120% of the resting motor threshold.

6.3.5 Transcranial Direct Current Stimulation

tDCS was delivered through two saline soaked sponge surface electrodes (secured to the scalp using an elasticated cap) using a programmable direct current stimulator (HDCkit, Newronika, Milan, Italy). The active and reference electrodes were 35 cm^2 and 71 cm^2 in size, respectively. In order to blind both participant and researcher to stimulation type, the current direction was pre-programmed by researchers not involved with data collection or analysis (Gandiga et al., 2006). The active electrode was positioned over F3 using the international 10-20 positioning system whilst the reference electrode was placed over the right supra-orbital region. In the active stimulation conditions, a current intensity of 1.5 mA was delivered for 15 minutes (current density under the active electrode = 0.043 mA/cm^2). In the sham conditions, current was delivered for 90 s. In order to ensure participants remained blind to stimulation type, current was ramped on and off for 15 s at the start of each stimulation (Gandiga et al., 2006).

6.3.6 EMG and Force Recording

Finger maximum voluntary contraction was then measured using a hand held dynamometer. Participants rested their right arm with the lateral side of the ulna resting against a table, their hand resting on a non-conductive rubber mat and their wrist supported by a gel pad. Participants held the dynamometer with the thumb, index and middle fingers. Participants were asked to maximally contract the thumb and index finger and the resultant force was recorded as the maximum voluntary contraction (MVC). Subsequently, 10% of the MVC (10%MVC) was calculated and a visual representation of the target force output was displayed in Labchart to enable participants to accurately produce the required force during TMS.

6.3.7 Cognitive Task

The 2-back working memory task was chosen as the cognitive task as task performance increase activation of prefrontal cortex and 2-Back performance has been shown to be mediated by application of tDCS (Zaehle et al., 2011). Stimuli were presented using the DMDX software (University of Arizona, Tucson, USA). Participants were presented with a sequence of 100 letters (A-H) in a pseudo-randomised order. The letters were in white text against a black background, and were displayed for 500 ms with a between stimulus interval of 2000ms. The participants were asked to press a key on a computer keyboard with their left hand when the letter displayed on the screen matched the letter displayed two stimuli previously (“2-back”). There were 20 target stimuli in each 100 letter set. The number of correct answers and errors pre and post stimulation in each trial were recorded. The error ratio was then calculated using the previously described methods (see General methods, Equation 4).

6.3.8 Experimental Design

Following familiarisation, individuals participated in three trials. At the start of each trial the hotspot, TMS intensity and MVC were determined. The force equivalent to 10% of MVC (10%MVC) was calculated and marked on Labchart. Subsequently, participants received eight stimulations (separated by 3 s) at rest and three stimulations when contracting at force equal to 10%MVC (after 2 s of contraction). Participants were then asked to perform the 2-back task. After these baseline measurements, participants received anodal, cathodal or sham tDCS of prefrontal cortex, with each trial separated by a period of $\geq$7 days (Nitsche et al., 2008). The current direction order (anodal, cathodal or sham) was pseudo-randomised across participants. After tDCS, participants again received TMS at rest and during 10%MVC, and then performed the 2-back task again.

6.3.9 Data analysis

The effect of stimulation on MEP amplitude at rest and during MVC, and the percentage of correct answers and errors was examined using a two way repeated measures ANOVA (stimulation condition [anodal, cathodal, sham] x time [pre stimulation, post stimulation]). Significant effects were followed up using Bonferroni-corrected pairwise comparisons. Partial eta squared (ηp) was used as a measure of effect size for main and interaction effects and Cohen's d_{av} (d) was used for pairwise comparison effect sizes (Lakens 2013).

In order to examine the relationship between change in corticospinal excitability and change in cognitive task performance, change in MEP amplitude at rest and change in error ratio were calculated using the following equation.

Equation 8. Change in dependent variables after stimulation

$$Post\ Stimualtion\ - Pre\ Stimualtion$$

Subsequently, the relationships between change in MEP amplitude at rest, and change in error ratio was analysed using Pearson's correlation coefficent with bootstrap 95% confidence intervals. Statistical significance was set at $p \leq 0.05$.

6.4 Results

Pre and post stimulation MEP amplitude (mV) and error ratio at rest and during the 10% MVC, and the MVC (N) are illustrated in Table 8.

Table 8. Mean ± SD, MVC (N) and error ratio (%), pre and post tDCS

		Anodal	Cathodal	Sham
MVC (N)	Pre	1.02±0.36	1.02±0.23	0.93±0.30
	Post	1.09±0.50	1.00±0.20	0.91±0.26
Error ratio (%)	Pre	10.0±8.8	10.5±9.8	21.0±13.9
	Post	6.0±4.6	9.5±10.1	13.0±12.5

MEP; motor evoked potential, MVC; maximum voluntary contraction

6.4.1 Effect of tDCS on Corticospinal Excitability

There was no main effect of stimulation ($F_{(2,18)}$=0.3, *p*=0.738, *np*=0.033) or time ($F_{(2,18)}$=2.5 *p*=0.145, *np*=0.033) on MEP amplitude at rest. There was a significant interaction between stimulation condition and time on MEP amplitude at rest ($F_{(2,18)}$=5.5, *p*=0.014, *np*=0.380) where MEP amplitude was significantly lower after cathodal tDCS (*p*=0.009, *d*=0.5, Figure 20). There was no significant difference in MEP amplitude at rest after anodal (*p*=0.191) or sham tDCS (*p*=0.371). There was no main effect of stimulation ($F_{(2,18)}$=0.8, p=0.475, *np*=0.079) or time ($F_{(2,18)}$=2.1, *p*=0.174, *np*=0.195) on MEP amplitude during 10%MVC and there was no interaction between stimulation condition and time ($F_{(2,18)}$=0.1, *p*=0.953 *np*=0.005).

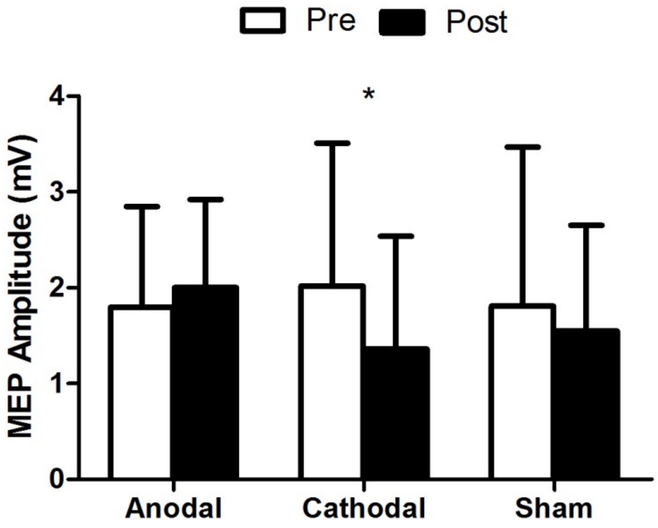

Figure 20. Mean MEP amplitude (%) pre and post stimulation. Error bars represent 1SD. * Signifies a difference pre to post tDCS.

6.4.2 Effect of tDCS on Cognitive Task Performance

There was a no main effect of stimulation condition ($F_{(2,18)}$=3.3, *p*=0.059, *np*=0.270) or time ($F_{(2,18)}$=2.6, *p*=0.139, *np*=0.227) on error ratio and there was no interaction between stimulation condition and time ($F_{(2,18)}$=1.7, *p*=0.202, *np*=0.163).

6.4.3 The Relationship between the Effects of tDCS on Corticospinal Excitability and Cognitive Task Performance

There was no correlation between change in error ratio and change in MEP amplitude at rest after anodal tDCS (*r*=-.036 [0.35, -0.81], *p*=0.302). There was also no significant correlation between number of correct answers and change in MEP amplitude at rest after cathodal tDCS (*r*=-0.0.31 [0.78, -0.40], *p*=0.392).

6.5 Discussion

The primary aim of this study was to examine the effects of tDCS of prefrontal cortex on corticospinal excitability and cognitive task performance. Cathodal prefrontal tDCS reduced corticospinal excitability at rest, but there was no effect of anodal tDCS. There was also no effect of tDCS on cognitive task performance. The secondary aim of this study was to examine the relationship between the effects of tDCS on cognitive task performance and corticospinal excitability. There was no relationship between the effects of anodal tDCS on both cognitive task performance and corticospinal excitability at rest. These findings indicate that prefrontal tDCS may influence the activity of neural motor networks, but there is no relationship between the effects of tDCS on cognitive task performance and corticospinal excitability.

6.5.1 Effect of Prefrontal tDCS on Corticospinal Excitability

In the present study, prefrontal cathodal tDCS reduced corticospinal excitability at rest, however there was no effect of anodal tDCS. These findings extend recent studies using tDCS (Vaseghi et al., 2015a) and TMS (Hasan et al., 2013; Tunovic et al., 2014) which reported that modulation of prefrontal activity influences corticospinal excitability. Prefrontal tDCS appears to alter activity in remote functionally and anatomically connected brain regions and networks (Stagg et al., 2013; Keeser et al., 2011a). A number of studies using TMS have shown that prefrontal cortex and motor cortex maybe functionally connected. Civardi et al. (2001) reported reduced MEP amplitude when paired pulse TMS was used to condition prefrontal cortex before motor cortex stimulation. More recently, Hasan et al. (2013) described task and muscle specific modulation of corticospinal excitability after prefrontal cortex stimulation. Hasan et al. (2013) reported that stimulation of prefrontal cortex increased excitability when participants were required to freely choose a response, but inhibited when the response was externally provided. Using tDCS, Vaseghi et al. (2015) reported a reduction in corticospinal excitability at rest following prefrontal tDCS, and suggested that prefrontal tDCS activates a motor network which includes the prefrontal, premotor and motor cortices. As in the present study, Boros et al. (2008) reported no effect of anodal tDCS on corticospinal excitability at rest. It is not clear why cathodal, but not anodal, prefrontal tDCS modulates corticospinal excitability. Although speculative, it is possible that prefrontal cathodal tDCS influences the excitation/inhibition balance in remote cortical motor areas. Using paired-pulse TMS, where the active stimulation is preceded by a sub-threshold conditioning pulse, it is possible to examine interneuron facilitation and inhibition (Hallett, 2007). Future research should therefore examine the effect of cathodal prefrontal tDCS on intracortical inhibitive and facilitative influences on corticospinal excitability.

Unexpectedly, we found no effect of prefrontal tDCS on MEP amplitude during a submaximal force production task. Recent evidence has suggested that prefrontal cortex is involved in the monitoring of force output during a submaximal force production task (Mandrick et al., 2013), and the effect of prefrontal cortex stimulation on corticospinal excitability is dependent on temporal and muscular demands of a concurrently performed motor task (Hasan et al., 2013), suggesting that prefrontal cortex influences neural motor networks when attention is required for task performance. In these circumstances, prefrontal tDCS might be expected to influence MEP amplitude during submaximal contraction. Hasan and colleagues (2013) suggested that the indirect connection between prefrontal cortex and motor cortex (and thus the corticospinal tract) is influenced by other ascending inputs during task performance, which may attenuate the excitatory and inhibitory influence of prefrontal cortex on corticospinal excitability. Thus, although activation of prefrontal cortex may increase during a submaximal force production task, this may not necessarily equal an increased influence on interconnected neural networks, including motor cortex and corticospinal tract.

6.5.2 The Relationship between the Effects of tDCS on Cognitive Task Performance and Corticospinal Excitability

The second aim of this study was to examine the relationship between the effects of tDCS on cognitive task performance and corticospinal excitability. In contrast to our hypothesis, there was no effect of tDCS on working memory performance. Only cathodal tDCS altered corticospinal excitability and there was no relationship between this effect and the effect of tDCS on cognitive task performance.

A number of studies have reported improvements in working memory performance following prefrontal tDCS. An early study by Fregni et al., (2005) reported improved accuracy in 3-back performance following anodal tDCS whilst Zaehle et al., (2011) reported improvements and reductions in 2-back performance following anodal and cathodal tDCS, respectively. In contrast to these reports, here there was no effect of either anodal or cathodal tDCS on 2-back performance. In accordance with these results, there is growing evidence indicating substantial inter-individual variability in the behavioural response to tDCS (Jacobson et al., 2012; Wiethoff et al., 2014; Horvath et al., 2015). The cause of this variation remains unclear, but several mechanisms have been proposed including variation in genotype (Nieratschker et al., 2015) skeletal and brain anatomy (Opitz et al., 2015) and sub-cutaneous fat around the head (Truong et al., 2013). Variation in cognitive effects may also be dependent on the state of underlying neural populations during stimulation (Learmonth et al., 2015), baseline task performance characteristics (Tseng et al., 2012; Benwell et al., 2015) and individual motivation (Jones et al., 2015).

Bortoletto et al. (2015) reported a relationship between the behavioural and physiological effects of motor cortex tDCS. Although Bortoletto and colleagues (2015) framed these findings against stochastic models of tDCS effects, it is possible that a relationship between physiological and behavioural responses to stimulation also reveals anatomical and physiological influences on tDCS. In the present study, only cathodal tDCS altered corticospinal excitability, however there was no relationship between this change and the effect of tDCS on working memory performance. These results indicate that although prefrontal cortex appears to influence activity of the corticospinal system, these effects are not related to the effects of tDCS on cognition. However, it is possible that the nature of the cognitive task employed here (a seated N-back task) may have influenced these results. Bortoletto et al. (2015) employed a thumb abduction motor learning task, and reported a correlation between the effects of tDCS on learning and corticospinal excitability. It could be argued that this task would require a greater degree of cognitive control over motor actions than a 2-back task. It is therefore possible that there may be a similar relationship between the effects of prefrontal tDCS on dual-task gait (which requires cognitive control of motor output), and corticospinal excitability, and this should be a topic for future research.

6.6 Conclusion

In conclusion, here we report that prefrontal cathodal tDCS reduced corticospinal excitability, suggesting that changes in cognitive-motor tasks following prefrontal tDCS may be due to changes in a neural motor network. In contrast to previously reported results, there was no effect of tDCS on working memory performance. In addition, there was no relationship between the effects of tDCS on corticospinal excitability or cognitive task performance. These results indicate that prefrontal tDCS exerts effects on remote motor networks, suggesting a possible mechanism by which prefrontal cortex may exert control over dual-task walking.

7. Effect of Prefrontal tDCS on Dual-Task Gait Performance is Dependent on Walking Modality and Task Difficulty

7.1 Abstract

The influence of walking modality and perceived task difficulty on the effects of tDCS on dual-task gait performance was examined in 15 right handed males. Additionally, the coordination between gait and cognitive task performance was examined during treadmill dual-task walking. Participants performed dual-task walking on a motorised treadmill and over-ground, both before and during application of prefrontal tDCS. A median spilt was performed on the participants using their ratings of perceived task difficulty during dual-task walking. The effects of tDCS were influenced by walking modality and perceived task difficulty. During over-ground walking only, anodal tDCS increased the dual task cost on gait only for those who found the dual-task hardest. There was no effect of tDCS on treadmill dual-task gait. Participants appeared to coordinate walking and cognitive task performance, with significantly more response being made during the initial swing phase than during terminal swing or double limb support phases. The possible implications of these findings for the interpretation of dual-task effects on gait, and the efficacy of tDCS to examine neural correlates of walking, are discussed.

7.2 Introduction

Prefrontal cortex has been implicated in dual-task gait performance. Age-related changes in dual-task gait performance may be related to reduced prefrontal cortical volume and reduced brain function (Montero-Odasso and Hachinski, 2014). Imaging studies reveal that prefrontal cortex activation increases during dual-task gait (Holtzer et al., 2011; Doi et al., 2013; Mirelman et al., 2014) and stimulation of prefrontal cortex using transcranial direct current stimulation (tDCS) changed STV during treadmill dual-task gait (Wrightson et al. 2015b, Chapter 5). Because changes in STV are interpreted as changes in the allocation of cognitive resources to gait (Lövdén et al., 2008), prefrontal tDCS appears to influence the allocation of cognitive resources during dual-task gait (Wrightson et al. 2015b, Chapter 5). In contrast to these findings, Zhou et al. (2014) reported no effect of tDCS on step variability during over-ground dual-task gait. This discrepancy may be explained by the use of different walking modalities in both studies. STV increases during over-ground dual-task gait (Beauchet et al., 2005b; Kelly et al., 2013; Simoni et al., 2013) and decreases during treadmill dual-task gait (Lövdén et al., 2008; Schaefer et al., 2010) suggesting that allocation of cognitive resources to task performance may differ across walking modalities (Wrightson et al., 2016, Chapter 4). The effects of tDCS on dual-task gait may therefore be dependent on the walking modality.

Although early studies often report uniform, polarity dependent, effects of tDCS on cognitive function (see Kuo and Nitsche 2012 for a review), more recent evidence suggests that tDCS may be mediated by inter-individual physiological and psychological characteristics. Inter-individual variation in cranial and brain anatomy (Bikson et al., 2012), genetics (Nieratschker et al., 2015) and neurophysiology (Krause et al., 2014) have all been suggested to mediate tDCS effects. Bortoletto et al., (2015) reported a relationship between the effects of tDCS on behaviour (motor learning) and corticospinal excitability, suggesting that physiological responses of tDCS may be able to help determine individual behavioural responses to stimulation. However, it is not clear whether a relationship exists between the effects of prefrontal tDCS on dual-task gait and corticospinal excitability.

Individual task performance characteristics may also influence the effects of tDCS on cognitive function (Li et al., 2015). Recent models highlight the state dependent nature of tDCS, where the effects of stimulation are biased by the underlying activity of the neural tissue and networks being stimulated (see Bestmann et al. 2014 for a review). Individual differences in task performance are suggested to influence tDCS because the relative difficulty of the task may be is related to the activity of the stimulated neural structures (Learmonth et al., 2015; Benwell et al., 2015). At present, there has been no examination of the role of relative task difficulty on the effects of tDCS on dual-task gait.

The dominant paradigm used in dual-task gait study involves separating gait and cognition into independent components competing for resources and individually examining task performances in both (Woollacott and Shumway-Cook, 2002). However, it may not be accurate to consider cognition and motor processes as separate. Dual-tasks can exhibit a high degree of cooperation between motor and cognitive processes through entrainment (Klapp et al., 1998; Franz et al., 2001). The observed coordination of two motor tasks and between visual and motor processes requires input from high-level cognitive systems, and changes in the allocation of attention/cognitive resources to the coordinated tasks influences the coordination pattern (Monno et al., 2002; Huys and Beek, 2002). To date there has been no attempt to examine whether task coordination between the cognitive and walking task exists during dual-task gait. It is possible that, as with bi-manual dual-tasks (Klapp et al., 1998; Franz et al., 2001), coordination exists between the performance of the two tasks, and that allocation and prioritisation of cognitive and attentional resources to each component (walking and cognitive) influences this coordination.

Although tDCS of prefrontal cortex has been shown to affect STV during dual-task gait, results are inconsistent across different walking modalities (Wrightson et al. 2015; Zhou et al. 2014). The effects of tDCS may also be dependent on inter-individual differences in perceived task difficulty. Therefore, the aim of this study was to examine whether the effects of tDCS on dual-task gait performance were dependent on the walking modality and relative task difficulty. We predicted that both walking modality and task difficulty would mediate the effects of tDCS on dual-task gait. We also examined whether cognitive and gait performance during dual-task gait were coordinated, and whether prefrontal tDCS influenced this relationship. Because task performance is coordinated during bi-manual dual-tasks (Klapp et al., 1998; Franz et al., 2001), we predicted that gait and cognitive task performance would be coordinated during dual-task gait, whereby participants would articulate a greater number of answers at a given phase of the gait cycle.

7.3 Method

7.3.1 Participants

Fifteen right handed males (mean ± SD age: 21.7 ± 2.2 years) volunteered to participate in the study. Prior to participation all participants gave written informed consent and were screened for medical contra-indications to tDCS using self-completed health questionnaires. All procedures were approved by the local University ethical committee and were conducted in accordance with the declaration of Helsinki.

7.3.2 Gait Analysis

Temporal gait variables were recorded using a portable gait analysis system which consisted of three body worn sensors, each containing a gyroscope (OPAL, APDM, Portland, USA). The sensors transmitted their data online to a wireless receiver linked to a personal computer running the Mobility Lab software package (version 1, APDM, Portland, USA) where the data were filtered and underwent online bias removal. Three separate temporal events, heel strike, toe off and mid-swing were identified by the Mobility Lab software through changes in shank angular velocity (Salarian et al., 2004). Stride time was calculated as the mean time between successive heel strikes across both legs. STV was calculated as the coefficient of variation of mean stride time. During over-ground walking, STV recorded during turns was removed from analysis. Turns were identified using the angle of trunk rotation in the yaw axis by a previously described algorithm in the mobility lab software (Salarian et al., 2010).

7.3.3 Cognitive Task

Starting from a number 1000-1999, pseudo-randomised in Microsoft Excel (Version 2013, Microsoft Corporation, Redmond, USA), participants were required to verbally subtract in sevens for 120 s. The performance was recorded using the Videography software package (Appologics, Eurasberg, Germany) running on a tablet computer (iPad, Apple, Cupertino, USA) which was synchronised to the gyroscope data through Mobility Lab. The video was analysed offline using the Premier pro software package (Version CS5, Adobe, San Jose, USA). Correct and incorrect answers were recorded (including those given during turns) and the ratio of errors to correct answers (error ratio) was then calculated as described previously (see Equation 5, General Methods).

7.3.4 Transcranial Direct Current Stimulation

Transcranial stimulation was delivered through rubber electrodes placed in saline soaked sponges secured onto the head using an elastic hair net. Current was delivered via a programmable battery driven stimulator (HDCkit, Newronika, Milan, Italy) which was secured onto their waist using an elastic strap. Participants received anodal, cathodal or sham tDCS in a counterbalanced order. Both experimenter and participant were blind to the stimulation condition. The active electrode was placed at F3 using the 10-20 EEG system and the reference electrode was placed over the contralateral supra-orbital region. The active electrode was 35 cm^2 and the reference electrode was 72 cm^2 in size. The applied current was 1.5 mA, giving a current density of 0.043mA/cm2 under the active electrode and 0.021 mA/cm^2 under the reference electrode. Current was ramped up for 15 s in all conditions. For the anodal and cathodal conditions stimulation was applied for 15 minutes. For the sham condition, current was switched off after 30 s.

7.3.5 Transcranial Magnetic Stimulation

Assessment of corticospinal excitability was performed using single pulse TMS, delivered using a Magstim200 stimulator which has a maximum output of 2.5 Tesla (Magstim Company, Whitland, UK) with a flat figure of eight coil (7 cm diameter) placed tangentially to the scalp and at an angle of 45° to the midline. Correct coil placement determined was using the following method: after marking the vertex, the "hotspot" for TMS was identified as the area of left motor cortex which when stimulated using a stimulator intensity of 60% of maximum, resulted in the greatest MEP measured by EMG in the contralateral FDI. All stimulations were delivered with the coil placed at this hotspot. Subsequently, the stimulator intensity which resulted in an EMG response of below 0.05 mV in four of eight stimulations (resting motor threshold) was determined by decreasing stimulator intensity in 1% increments from 70% of maximum stimulator output. All subsequent TMS were delivered at 120% of the resting motor threshold.

7.3.6 Task Coordination

Task coordination between the articulated answers and temporal gait markers was assessed during treadmill dual-task gait. The timestamp of three temporal events, toe off, mid swing and heel strike for both legs during treadmill dual-task gait was exported from Mobility Lab to Microsoft Excel. The gait cycle was then divided into three parts for both legs: initial swing (the time period between toe off to mid-swing), terminal swing (the period between mid-swing to heel strike) and Double-Limb Support (the period after heel strike where both limbs are in contact with the treadmill belt). The timestamp on which the last two digits of each number was articulated in the cognitive task was recorded using Premier pro. The percentage of the total answers that occurred in each phase of the gait cycle were then recorded.

7.3.7 Procedure

Initially participants were familiarised with the walking and cognitive tasks, and their preferred treadmill walking speed was determined using a well-established protocol (Wrightson et al., 2016). Subsequently, participants attended the laboratory on three occasions, separated by at least 48 hours. During each session participants first performed the serial subtraction task whilst standing, which was used as the single-task condition for the cognitive task. They then performed 120 s of walking only (single-task) followed by 120 s of walking whilst performing the serial subtraction task (dual-task) both over-ground and on a treadmill (CLST, Life Fitness, Cambridge, UK) in a counter balanced order. The over-ground walking was performed on a 12 m walkway with one metre turning zones marked at each end. During over-ground walking, participants were asked to walk at their usual comfortable walking speed. There was a 15 s break between each walking trial. Participants performed the four walking trials twice, initially without tDCS (pre-stimulation) and then subsequently whilst receiving tDCS. After the pre-stimulation walking trial was complete, the electrode sponges were changed and reapplied in the same position. The stimulator was then turned on. After three minutes of stimulation, participants again performed the serial subtraction task whilst standing and proceeded to perform the four walking trials as before. During the stimulated trial, electrode placement was checked. If the electrodes had drifted during the walking trial, the stimulator was turned off and the electrodes were adjusted before the stimulator was turned back on. This happened in 6 of 360 walking trials. After each dual-task walking trial, participants were asked to rate how difficult they found the trial, using the Borg CR10 scale (Borg, 1998). Participants were encouraged to describe the task difficulty of the combined walking and counting, rather than either one of the two tasks in isolation.

In two separate trials, corticospinal responses to prefrontal tDCS were examined. Corticospinal excitability at rest was measured using TMS, pre and post anodal and cathodal prefrontal tDCS (see Chapter 6 and General Methods for details).

Stimulation order was counterbalanced across participants. tDCS was delivered using the same stimulation parameters as the main trials.

7.3.8 Data Analysis

All data are reported as mean ± SD. We examined the effect of walking modality, tDCS and perceived task difficulty on STV and cognitive task error ratio during dual-task gait, as well as the dual-task cost on STV and error ratio. The dual-task cost is a measure of change from single to dual-task conditions (Kelly et al., 2010) and was calculated as described previously (General Methods; Equation 6 for STV, Equation 7 for error ratio)

Initially, the perceived task difficulty for each walking modality was collected for all pre-stimulation walking trials. The mean task difficulty for all treadmill and over-ground walking trials were compared using a Wilcoxon signed rank test. A median split was then performed on the mean of the pre-stimulation difficulty scores and participants were separated into two groups: LOW, the poorest performers and HIGH, those who performed the task the best. For both over-ground and treadmill walking, there were seven participants in the HIGH group, and eight in LOW. The same participants were in each group for both walking modalities.

The effects of walking modality and perceived task difficulty on STV and the dual-task cost on STV were analysed for each using a four-way mixed design ANOVA with three within subject variables (walk [over-ground, treadmill] x stimulation condition [anodal, cathodal, sham], x time [pre stimulation, post stimulation]) and task difficulty group as the between subject variable.

Due to equipment error, it was not possible to record the cognitive task data for all participants. Therefore, for the error ratio and task coordination analysis, n = 10 for the anodal and sham conditions. There were too few complete data sets to analyse the effects of cathodal tDCS. The effects of walking modality and tDCS on cognitive task performance were thus analysed a four-way mixed design ANOVA (walk [over-ground, treadmill] x stimulation condition [anodal, sham], x time [pre stimulation, post stimulation] x task difficulty group).

Changes in MEP amplitude and over ground and treadmill STV pre and post anodal tDCS were calculated using the following equation (Nitsche and Paulus, 2000):

Equation 8. Change in MEP amplitude and the duak task cost on STV

$$\frac{Pre\ stimulation\ value}{Post\ stimulation\ value}$$

Changes in MEP amplitude were not normally distributed, so the effects of anodal and cathodal tDCS were compared using a Wilcoxon signed rank test. The relationship between change in MEP amplitude and in the cost on STV was examined using Spearman's correlation coefficient with bootstrap 95% confidence intervals.

The effect of walking modality and tDCS on task coordination were analysed using a four way repeated measure ANOVA (stimulation condition [anodal, sham], x time [pre stimulation, post stimulation] x leg [right, left] x gait phase [initial swing, terminal swing, double-limb support].

Significant effects were followed up using Bonferroni-corrected pairwise comparisons. Partial eta squared (ηp) was used as a measure of effect size for main and interaction effects and Cohen's d_{av} (d) was used for pairwise comparison effect sizes (Lakens 2013). Statistical significance was set at $p \leq 0.05$.

7.4 Results

7.4.1 Gait analysis

The mean ± SD of strides, mean stride time (s) and perceived task difficulty (Borg CR10) for both walking modalities (averaged cross all the stimulation conditions) are shown in Table 9. There was no significant difference in perceived task difficulty between over-ground and treadmill dual-task gait (T=0.814, p=0.414).

Table 9. Mean ± SD number of strides, stride time (s) and median ± IQR perceived task difficulty (Borg) for both walking modalities

	Over-ground Walking	Treadmill Walking
Strides	68±6	100±6
Stride Time (s)	1.14±0.06	1.16±0.05
Perceived Task difficulty	4±2	4±2

7.4.2 Effect of Walking Modality on Stride Time Variability

Figure 21 shows the effects of walking modality on STV. There was a significant main effect of walking modality on STV ($F_{(1,13)}$=51.6, p<0.001, ηp=0.799). STV was significantly higher during over-ground walking compared to treadmill walking (MD=0.95%). There was also a significant main effect of walking modality on the dual-task cost on STV ($F_{(1,13)}$=19.2, p=0.001, ηp=0.596) where the dual-task cost on STV was significantly higher during over-ground walking compared to treadmill walking (MD=20.38%).

7.4.3 Effect of Walking Modality on Cognitive Task Performance

There was no effect of walking modality on error ratio ($F_{(1,8)}$=0.3, p=0.634, ηp=0.030) or the dual-task cost on error ratio ($F_{(1,8)}$=0.4, p=0.857, ηp=0.004)

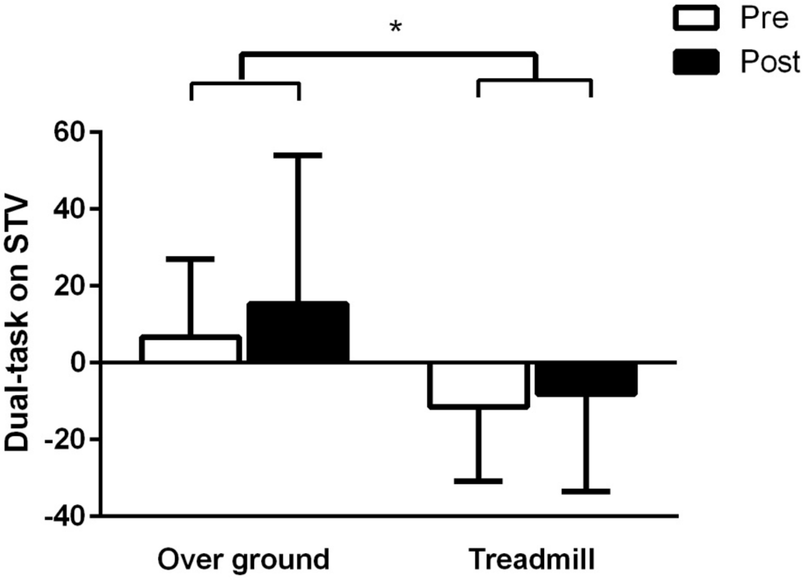

Figure 21. Mean dual-task cost on stride time variability (%) pre and post stimulation, averaged across all three stimulation conditions. Error bars represent 1SD. * Signifies a difference between walking modalities

7.4.4 Interaction Between Walking Modality and tDCS on STV

There was no significant interaction effect between stimulation condition, walking modality and time on STV ($F_{(2,26)}$=0.1, p=0.929, ηp=0.006) or on the dual-task cost on STV ($F_{(2,26)}$=0.4, p=0.960, ηp=0.003).

7.4.5 Interaction Between Walking Modality and tDCS on Cognitive Task Performance

There was also no significant interaction effect between walking modality, stimulation condition and time on error ratio ($F_{(1,8)}$=0.1, p=0.774, ηp=0.011) or the dual-task cost on error ratio ($F_{(1,8)}$=0.6, p=0.451, ηp=0.073).

7.4.6 Interaction Between Perceived Task Difficulty, Walking Modality and tDCS on STV and Cognitive Task Performance

There was a significant four-way interaction between walking modality, stimulation condition, time and task difficulty on STV ($F_{(2,26)}$=3.6, p=0.041, ηp=0.217). In LOW, follow up revealed a trend (MD=0.28%, p=0.071, d=0.3) for an increase in STV after sham tDCS during over-ground walking. There were no other pre to post differences in STV after anodal or cathodal stimulation, in either difficulty group. There was also a significant four-way interaction between walking modality, stimulation condition, time and task difficulty group on the dual-task cost on STV ($F_{(2,26)}$=6.2, p=0.006, ηp=0.322). During over-ground walking, in HIGH, the dual-task-cost on STV during over-ground walking was higher after anodal tDCS (MD=37.35%, p=0.035, d=1.0, Figure 22) whilst in LOW there was a trend (MD = 27%, p=0.052, d=0.8) for the dual-task cost on STV to increase after sham stimulation but not after either active stimulation condition. During treadmill walking, there were no pre to post stimulation differences in STV or the dual-task cost on STV.

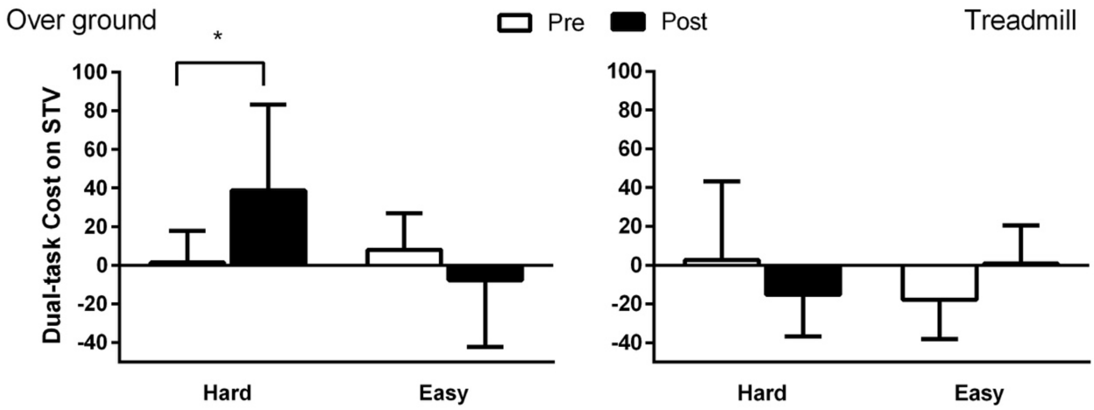

Figure 22. Mean dual-task cost on STV pre and post anodal tDCS during both over-ground (left) and treadmill (right) walking. Error bars represent 1 SD. * Signifies a difference pre to post stimulation.

7.4.7 Interaction Between Perceived Task Difficulty, Walking Modality and tDCS on Cognitive Task Performance

There was no significant interaction between walking modality, stimulation condition, time and task difficulty group on error ratio ($F_{(1,8)}$=3.9, *p*=0.085, *ηp*=0.325) or the dual-task cost in error ratio ($F_{(1,8)}$=0.787, *p*=0.451, *ηp*=0.073).

7.4.8 The Relationship between the Effects of tDCS on Stride Time Variability and Corticospinal Excitability

For anodal tDCS, there was a significant negative correlation between change in MEP and change in dual-task cost on STV (*r*=-0.61 [-0.86, -0.17], r^2=0.37, *p*=0.016) during treadmill walking (Figure 23) but not over ground walking (*r*=0.18, *p*=0.524). For cathodal tDCS, there was no significant relationship between change in MEP and the dual task cost on STV during treadmill walking (*r*=-0.38, *p*=0.524) or over ground walking (*r*=0.08, *p*=0.791).

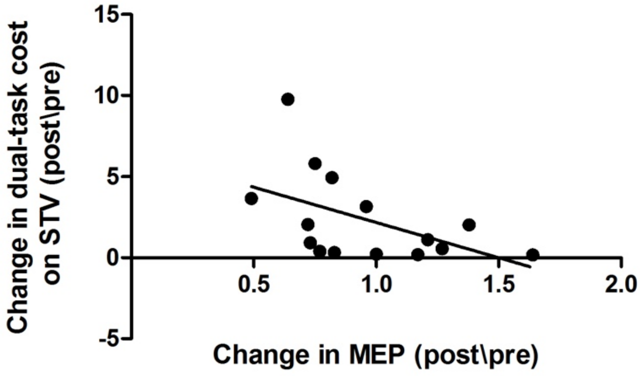

Figure 23. Relationship between change in corticospinal excitability (MEP) and the dual task cost on STV.

7.4.9 Effect of tDCS on Task Coordination

There was an effect of gait cycle on task coordination ($F_{(2,18)}=57.5$, $p<0.001$, $\eta p=0.865$, Figure 24) where participants articulated significantly more answers during the initial swing phase than during the terminal swing (MD=8.8%, $p<0.001$, $d=1.1$) or double-limb support phases (MD=13.9%, $p<0.001$, $d=1.9$). Percentage of articulated answers was also significantly higher during the terminal swing phase than during double-limb support (MD=5.1%, $p=0.030$, $d=0.8$). There was no main effect of stimulation condition ($F_{(1,9)}=0.7$, $p=0.427$, $\eta p=0.071$), time ($F_{(1,9)}=0.9$, $p=0.363$, $\eta p=0.093$) or leg ($F_{(1,8)}=4.4$, $p=0.064$, $\eta p=0.331$) and no interaction effects (all $p>0.05$).

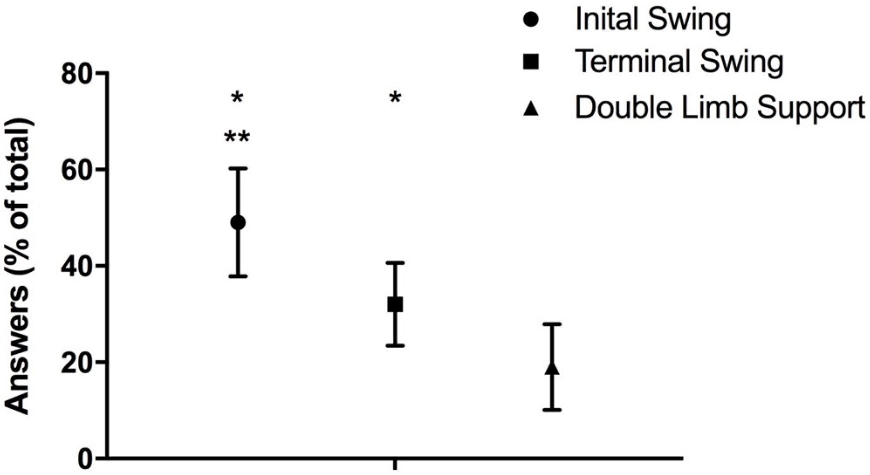

Figure 24. Answers articulated in each gait phase (%). Error bars are 1SD. * represents a significant difference in answers articulated compared to the double-limb support phase, ** represents significantly more answers articulated than during the terminal swing phase.

7.5 Discussion

The primary aims of the present study were to examine whether walking modality influences both dual-task gait and the effect of prefrontal tDCS on dual-task gait. As predicted, there was an effect of walking modality on both dual-task gait and on the effects of tDCS on dual-task gait, though results were dependent on the relative task difficulty of the dual-task. During over-ground walking only, the dual-task cost on STV increased after anodal tDCS for those who found the dual-task hardest. In those that found the task easier, STV and the dual-task cost on STV appeared to increase after sham, but not anodal or cathodal, tDCS. There was no effect of tDCS on dual-task gait performance during treadmill walking. These findings extend previous studies which have reported an effect of tDCS on dual-task gait (Zhou et al., 2014; Wrightson et al., 2015) by showing that the effects of tDCS on STV may be dependent on the walking modality and on inter-individual differences in task performance.

7.5.1 Effect of Walking Modality on Dual-Task Gait

In the present study, STV and the dual-task cost on STV were higher during over-ground walking compared to treadmill walking. The dual-task cost on STV during treadmill walking was negative, indicating that participants' gait became less variable during the dual-task compared to walking only. Conversely, the dual-task cost on STV was positive during over-ground walking, indicating an increase in gait variability during the dual-task. These findings are in accordance with a number of other studies where STV decreased during treadmill dual-task gait (Schaefer et al., 2010; Lövdén et al., 2008) and increased during over-ground dual-task gait (Beauchet et al., 2005b). A reduction in STV during dual-task gait is suggested to indicate increased automaticity, whilst an increase in STV may indicate an increased cognitive control of gait (Lövdén et al., 2008; Hausdorff, 2005). The disparity between the dual-task costs on STV across walking modalities seen here supports previous findings from Simoni et al. (2013) which indicated there may be a difference in the allocation of high level cognitive resources during dual-task gait between over-ground and treadmill walking.

Walking modality also influenced the effect of prefrontal tDCS on dual-task gait, there was an effect of tDCS on dual-task gait during over-ground walking but not on treadmill dual-task gait. Because changes in the allocation of cognitive resources to gait is suggested to result in changes to STV (Lövdén et al., 2008) these findings support the suggestion that prefrontal cortex is involved in the allocation of cognitive resources during dual-task gait performance (Wrightson et al., 2016). A recent model of prefrontal cortex function posits that prefrontal cortex is part of a distributed neural network (the fronto-parietal network) composed of richly connected neural hubs which flexibly alter their connectivity to other brain regions and networks in order to bias neural information relevant to the goals of a (or several) cognitive tasks (Cole et al., 2013). Here, the dual-task cost on STV differed between over-ground and treadmill walking, indicating differences in the allocation and prioritisation of cognitive resources across the two modalities. As prefrontal cortex is likely involved in this prioritisation (Milham et al., 2003; Cole et al., 2013), then it is reasonable to assume that prefrontal cortex activity may differ across walking modalities, leading to the different effects of prefrontal tDCS between over-ground and treadmill dual-task gait observed here.

7.5.2 Inter-individual Variability in Response to tDCS

Although these results add to the literature showing stimulation of prefrontal cortex influences dual-task gait performance, here there was no effect of tDCS on treadmill dual-task gait. These results are in contrast to our previous study where during treadmill dual-task gait, STV and the dual-task cost on STV were lower after anodal tDCS and higher after cathodal tDCS (Chapter 5). The reasons for this disparity are not clear, however this finding is an accordance with a recent systematic review which concluded that the effects of tDCS on cognition are not uniform and vary between individuals (Horvath et al., 2015). Proposed causes for these discrepancies include anatomical differences between participants, individual personality traits and differences in the ‘state’ of the neuronal populations being stimulated (Datta et al., 2012). Recent models of tDCS highlight the state dependent nature of stimulation effects (Bestmann et al., 2014). In accordance with these models, a number of researchers reported the influence of inter-individual task performance characteristics on tDCS effects (Tseng et al., 2012; Learmonth et al., 2015; Benwell et al., 2015). Because the effects of tDCS on dual-task gait performance were different between those who found the task hardest and those who found it easier, these results extend these findings by showing that perceived task difficulty influences the effects of tDCS on dual-task gait.

Another possible explanation for the discrepancy between these and previous results is differences in the stimulation protocol. The present study employed an online tDCS protocol where stimulation is delivered during task performance, whilst previously we employed an off-line procedure where the task is performed after stimulation cessation. Online stimulation is suggested to directly alter membrane properties of the neurons activated during the task, whilst offline stimulation leads to plasticity like changes to synaptic function in the stimulated neural areas (Stagg and Nitsche, 2011; Miniussi et al., 2013). Previous comparisons of online and offline stimulation have suggested they elicit different effects on cognitive functions (Wirth et al. 2011; Fertonani et al. 2014). The discrepancy between then results of this study and Chapter 5 may be due different states of the task relevant neural network during treadmill walking in the two studies. However, it is not clear why this would only affect treadmill walking.

There was a negative relationship between the effects of prefrontal anodal tDCS on treadmill dual-task gait and corticospinal excitability. These results indicate that in the participants for whom anodal tDCS increased corticospinal excitability, tDCS also reduced the dual-task cost on gait. The present results indicate a relationship between the dual-task and physiological effects of tDCS. Recent evidence suggests that only a third of participants respond to motor cortex tDCS in the canonical (anodal excites\cathodal inhibits) manner (Wiethoff et al., 2014) and a number of physiological and psychological influences on stimulation have been identified (Li et al., 2015). Bortoletto et al. (2015) reported that corticospinal response to motor cortex tDCS was correlated with behavioural changes following stimulation, indicating the individual corticospinal responses to tDCS may be related to behavioural changes following stimulation. Although the results here require replication in a larger sample, it appears as if the effects of prefrontal tDCS on corticospinal excitability may also be related to behavioural changes following stimulation. Using TMS to assess the effects of prefrontal tDCS on corticospinal excitability may thus allow the identification of responders and non-responders to stimulation. It should be noted however that there was no relationship between the effects of tDCS on over ground dual-task gait. Although the reason for this difference is unclear, it may indicate a difference between the underlying state of prefrontal cortex during stimulation between the two walking modalities, where the effects of stimulation during over ground walking are not as influenced by physiological factors which presumably underlie the modulation of corticospinal excitability by tDCS.

As predicted, there appeared to be coordination between gait and cognitive task performance. Participants made significantly more answers during the initial swing phases than during the terminal swing or during double-limb support phases. A number of researchers have reported coordination between bimanual dual-tasks (Jagacinski et al., 1988; Franz et al., 2001) and between respiration and locomotion (Amazeen et al., 2001; Villard et al., 2005). For the first time we have shown that participants appear to articulate their cognitive task answers at specific points in their gait cycle during dual-task gait. The mechanisms underlying this coordination are not clear, however. It is possible that the co-ordination between articulation and gait cycle may be due to the coordination between respiration and gait, with articulation occurring during specific periods in the respiration cycle. The co-ordination between locomotion and breathing may be affected by the gait-cycle phase, because changes in posture elicit different mechanical pressures on the breathing apparatus (Takano 1995). Initial swing occurs during the loading response to mid stance phases of the supporting (opposite) leg, (Levine et al., 2012) and this phase in the gait cycle may have mechanical implications for articulation of answers. However, the data presented here is for the articulation of the final two digits of each number only because the majority of calculations are performed on these numbers. It is not clear whether the proposed mechanical influence on articulation thus occurs during this phase of the gait cycle or earlier, for example during double-limb stance. Alternatively, the coordination between two manual tasks may be dependent on the availability cognitive resources (Monno et al., 2002). Interference between two bimanual tasks is reduced when the tasks are performed as a unitary coordinated task (Franz et al., 2001). It is thus possible that the coordination between gait and cognitive tasks here represents a cognitive strategy to reduce dual-task costs. However, because these effects were not influenced by prefrontal tDCS this seems be unlikely. Nonetheless, it is possible that more sophisticated measures based on the dynamics of both systems (for e.g.

Daffertshofer et al. (2004)) may provide a deeper understanding of the coordination between tasks during dual-task gait. Examination of dual-task coordination, and the possible influence of articulation on that coordination, using these methods is thus warranted. These limitations notwithstanding, these results indicate that participants coordinate task performance during dual-task gait. These findings may have implications for the interpretation of dual-task costs on gait. The dominant paradigm is to examine each task separately, however, the coordination seen in the present study suggests that analysis of performance in the whole task, that is cognitive and walking tasks together, may provide deeper insight into the nature of these dual-task effects.

7.6 Conclusion

This study extends previous work which indicated that prefrontal cortex is involved in the biasing and allocation of cognitive resources during dual-task gait by showing that the effects of prefrontal tDCS on dual-task gait are dependent on walking modality. Over-ground and treadmill walking appear to differ in their allocation of cognitive resources to walking during dual-task gait, and the effects of prefrontal tDCS was different across walking modalities, suggesting that they may place different demands on the neural systems which control dual-task gait performance. Furthermore, in the present study these effects were themselves influenced by inter-individual perceptions of task difficulty, supporting the growing body of literature that showing individual characteristics influence the effects of tDCS on cognition. Because the prioritisation of cognitive resources and prefrontal involvement may differ between over-ground and treadmill walking, researchers and clinicians should interpret the effects of treadmill dual-task gait with caution.

8. General Discussion

8.1. Introduction

The simultaneous execution of two tasks frequently leads to decrements in one or both task performances. During walking, the performance of a secondary task whilst walking, 'dual-task gait', has been shown to be related to brain function, and is a predictor of fall risk. The overall aim of this thesis was to examine the role of prefrontal cortex in the control of dual-task gait, using tDCS. Using the guided activation theory of prefrontal cortex function as a theoretical framework (Miller and Cohen, 2001), this aim was addressed in four experimental studies. The first study (Chapter 4) aimed to examine the role of cognitive task and walking speed on dual-task gait performance, to establish the dual-task cost on gait was influenced by cognitive domain or walking difficulty. The results of this study were used to inform the methods for the second study (Chapter 5) which aimed to examine the effect of prefrontal tDCS on dual-task gait at both preferred and slow walking speeds. In an effort to elucidate possible mechanisms by which modulation of prefrontal cortex activity may influence dual-task performance, the aim of the third study (Chapter 6) was to examine the effects of prefrontal tDCS on corticospinal excitability and replicate previously reported improvements in cognitive task performance. A secondary aim was to examine whether a relationship existed between induvial physiological and behavioural response to tDCS. The final study (Chapter 7) had two aims. The first was to examine the influence of walking modality (over-ground vs treadmill) on the effects of tDCS on dual-task gait. The second aim was to examine whether individuals coordinated cognitive task and gait performance during dual-task walking.

This chapter will review and discuss the main findings of this thesis. A possible role of prefrontal cortex in the control of dual-task gait is proposed, based on data from this thesis and previous models of prefrontal cortex function (Miller, 2000; Miller and Cohen, 2001). Furthermore, this general discussion will consider the contribution of this thesis to the current understanding of dual-task gait performance and the efficacy of tDCS to determine neural correlates of locomotion. The chapter concludes by considering the practical applications of the present findings, and the implications for future research.

8.2. Principal Findings

The aim of Chapter 4 was to examine the influence of cognitive task type and walking speed on dual-task gait performance, in order to inform the methodological approach for the thesis. Both working memory and mental arithmetic tasks are suggested to influence the cognitive control of gait (Al-Yahya et al., 2011), however no direct comparison of the effect of these tasks on dual-task gait performance had been performed. Slow walking increases stride to stride variability and may result in increased cognitive control of gait (Jordan et al., 2007; Beauchet et al., 2009c) and may thus represent a suitable paradigm for examining the role of prefrontal cortex in dual-task gait performance. However, the effect of slow walking on dual-task gait performance had not been investigated. The results of Chapter 4 revealed that, as expected, slow walking significantly increased STV and perceived task difficulty, suggesting greater demands on cognitive control processes during slow dual-task gait. Performance of both a mental arithmetic (serial subtraction) and working memory (2-back) task reduced STV at both normal and slow walking speeds. However, trunk RoM was greater during slow walking when performing the serial subtraction task than when performing the working memory task. Because the serial subtraction task appeared to influence dual-task gait more than the working memory task, these results provided a rationale for its use in subsequent studies. In addition, slow walking increased STV and perceived task difficulty, suggesting a greater degree of cognitive control. Thus, it was possible that prefrontal cortex activity differed between walking speeds. These results provided a rationale for examining the role of prefrontal cortex in the cognitive control of dual-task gait at both preferred and slow walking speeds in Chapter 5.

The aim of Chapter 5 was thus to examine the effect of prefrontal tDCS on dual-task gait performance at both preferred and slow walking speeds. Although Zhou et al., (2014) had revealed that anodal tDCS reduced the dual-task cost on gait, they had not examined the effect of cathodal tDCS, which may provide a more causal interpretation of effects (Vines et al., 2006). In addition, the cognitive task employed by Zhou and colleagues may have been too easy, as participants performed at ceiling in both active and sham conditions. Because task difficulty influences the allocation of cognitive resources during dual-task performance (Huxhold et al., 2006), this limits the interpretation of how prefrontal tDCS may influence dual-task performance. The results of Chapter 5 revealed a polarity dependent effect of stimulation on dual-task gait, where anodal tDCS decreased the dual-task cost on gait and cognitive task performance. Because a lower STV is suggested to represent increased automaticity of gait (Montero-Odasso et al., 2012), anodal prefrontal tDCS appeared to influence the allocation of cognitive control away from gait and toward cognitive task performance. From these results, it was concluded that prefrontal cortex appeared to be involved in the allocation of cognitive control across tasks during dual-task gait. This interpretation is in accordance with the guided activation theory of prefrontal cortex function, which posits that prefrontal cortex exerts cognitive control through the bias of on-going neural processes. Unexpectedly, there was no difference between the walking speeds.

The results of Chapter 5 indicated that tDCS may be suitable method to examine the role of prefrontal cortex in dual-task gait performance. Previous reports of dual-task performance changes following prefrontal tDCS interpreted effects using established models of dual-task costs which place the locus of dual-task control in prefrontal cortex (Zhou et al., 2014; Filmer et al., 2013). However, the results of Chapter 5 indicated that prefrontal cortex may exert dual-task control through modulation of ongoing task processes, in accordance with the guided activation theory (Miller and Cohen, 2001). A number of studies have reported functional connectivity between prefrontal cortex and the corticospinal system, suggesting this may be one method by which prefrontal cortex may exert cognitive control over motor actions (Hasan et al., 2013; Tunovic et al., 2014). The aim of Chapter 6 was to examine the effect of prefrontal tDCS on corticospinal excitability at rest and during an attention demanding motor task. Additionally, in order to examine the relationship between the physiological and behavioural effects of prefrontal tDCS, Chapter 6 also examined the relationship between the effects of prefrontal tDCS on cognitive task performance and corticospinal excitability. The results of Chapter 6 revealed that cathodal tDCS reduced corticospinal excitability at rest. These results suggested that prefrontal cortex influences motor network activity, highlighting a possible mechanism for the effects of prefrontal tDCS on dual-task gait performance.

In Chapter 5, there was a polarity dependent effect of tDCS on STV during treadmill walking. In contrast, Zhou et al., (2014) reported no effect of tDCS on step variability during over-ground dual-task gait. One possible cause of this discrepancy was the use of different walking modalities. In Chapter 4 and 5, STV was lower during treadmill dual-task walking than during usual walking, an effect also reported elsewhere (Schaefer et al., 2010; Lövdén et al., 2008). However, when compared to usual walking, during over-ground dual-task walking has been reported to increases STV (Beauchet et al., 2005b), indicating that cognitive control may be influenced by walking modality. Therefore, the aim of Chapter 7 was to compare both the roles of prefrontal cortex in both over-ground and treadmill dual-task gait. Because the relative difficulty of the task may alter both dual-task costs (Huxhold et al., 2006) and the effects of tDCS (Benwell et al., 2015), the influence of perceived task difficulty on the effect of tDCS on dual-task walking was also examined. The main finding was that both walking modality and perceived difficulty influenced the effects of prefrontal tDCS gait. During over-ground walking, prefrontal tDCS increased the dual-task cost on STV in those who found the task hardest, in those who found the task easiest, the dual-task cost on STV increased after sham tDCS but not after anodal or cathodal stimulation. Increases in STV may represent increased cognitive control of gait, indicating that cognitive control strategies differed between the two groups, and that prefrontal cortex appeared to be involved in the allocation of cognitive control across both. There was also a negative correlation between the effect of anodal prefrontal tDCS on the dual-task cost on gait and on corticospinal excitability: tDCS reduced the dual-task cost on gait most effectively in those individuals in whom it increased MEP size. These results suggest that individual variability in the effects of tDCS on dual-task gait may be related to individual variability in the physiological effects of stimulation.

Finally, Chapter 7 also examined the coordination between tasks during dual-task gait. The dominant dual-task gait paradigm separates motor and cognitive task performances, and this framework was used to interpret the results of Chapters 4 and 5. Although both tasks are performed simultaneously, it is unclear whether performances in both tasks are coordinated and whether dual-task gait should be evaluated as a single combined task. Chapter 7 examined whether there was coordination between cognitive and gait performance during dual-task walking. Results revealed task coordination during dual-task performance; participants articulated significantly more answers during the initial swing phase of the gait cycle than during terminal swing or double limb support, in either leg. Although the mechanisms underpinning this effect are not clear, it may be due mechanical influences on the capacity to articulate answers.

In the subsequent sections, the main implications of these findings are discussed. First, the proposed role of prefrontal cortex in the control of dual-task gait is presented, and the contribution of the results from this thesis will be compared against existing models of prefrontal function. Secondly, the implications of this thesis for the use of tDCS in examining the neural correlates of gait are discussed.

8.3. Implications of the Thesis

The following section will outline the implications of the results from the four experiential chapters of this thesis.

8.3.1. Prefrontal Cortex Biases Task Processing During Dual-Task Gait

Theories for the dual-task effect postulate that performance is controlled by a limited capacity central resource, and that dual-task demands exceed resource capacity (Tombu and Jolicœur, 2003). Early behavioural models of the dual-task effect posit that dual-task interference occurs because of a central bottleneck in response selection, resulting in serial task processing (Pashler, 1994). Subsequently, limited capacity models were proposed in an attempt to address the apparent simultaneous performance of two tasks after practice, which suggested that parallel processing of two tasks was achieved through the allocation of a limited pool of resources across both tasks (Miller et al., 2009). Activation of prefrontal cortex has long been linked to dual-task performance (Collette et al., 2005; Baddeley et al., 1997) and prefrontal cortex is frequently identified as the central resource controlling dual-task performance (Szameitat et al., 2002; Collette et al., 2005). There is also increased prefrontal cortex activation during dual-task walking (Holtzer et al., 2011; Mirelman et al., 2014) and Zhou et al. (2014) reported that prefrontal anodal tDCS reduced the dual-task cost on gait speed, indicating that prefrontal cortex may be involved in the control of dual-task gait. However, whilst these studies provide evidence of prefrontal cortex's involvement in dual-task gait control, they do not provide an indication as to the nature of that involvement.

Previous studies examining the effect off tDCS on dual-task performance have been interpreted using these limited capacity frameworks. A number of studies have reported changes in dual-task performance following prefrontal tDCS, and these changes have variously been ascribed to changes in to central processing (Filmer et al., 2013) or executive function capacity (Strobach et al., 2015). In dual-task gait, Zhou and colleagues (Zhou et al., 2014) reported a reduction in the dual-task cost on gait speed in healthy adults after prefrontal anodal tDCS, and suggested this was due to changes either in the availability of cognitive resources or increased processing speed, reducing a bottleneck effect as both tasks are processed in parallel. However, prefrontal cortex appears to be mostly recruited during serial response selection, whereas parallel response selection appears to preferentially activate the basal ganglia (Yildiz and Beste, 2015). Thus, it seems unlikely that modulation of prefrontal cortex excitability would necessarily result in an *increase* in the cognitive capacity required to processes two tasks in parallel.

In Chapter 5 prefrontal anodal tDCS reduced the dual-task cost on STV and on cognitive task performance. Because a reduction in STV occurred in conjunction with an improvement in cognitive task performance, the results of Chapter 5 indicate that anodal prefrontal tDCS altered the allocation of cognitive control resources across gait and cognitive task performance. Thus, rather than processing dual-task performance per se, it may be more accurate to conceptualise prefrontal cortex as a system which influences other task processing structures or networks, in accordance with the guided activation and flexible hubs frameworks (Miller, 2000; Miller and Cohen, 2001; Cole et al., 2012). The guided activation theory (Miller and Cohen, 2001) posits that prefrontal cortex biases neural processing based on task relevant goals and rules. A recent extension of this theory, the flexible hub theory, posits that prefrontal cortex is a member of fronto-parietal cognitive control network (FPN), characterised by its rapid and flexible alterations in regional connectivity during task performance (Cole et al., 2013). Cole and colleagues (Cole et al., 2010, 2012, 2013) and Miller and colleagues (Miller, 2000; Miller and Cohen, 2001) have suggested that prefrontal cortex/FPN exerts cognitive control through these rapidly shifting connections with other task relevant neural structures or networks, coordinating neural processing based on task requirements Within these frameworks, prefrontal cortex/FPN exerts cognitive control through bias of neural processing.

Support for the guided activation theory of prefrontal cortex function during dual-task gait, as opposed to the dual processing theory, can be found in the results of

Chapters 6 and 7. In Chapter 5 prefrontal tDCS altered the activity of the corticospinal system, whilst in Chapter 7 the effects of anodal prefrontal tDCS on corticospinal excitability and dual-task gait were correlated. Whilst this relationship may simply reflect anatomical influences on stimulation (covered in more details below), it is also possible that these data indicate that prefrontal cortex may influence motor behaviour through modulation of neural motor networks. Prefrontal cortex projects to dorsal premotor cortex, which in turn projects both to motor cortex and directly to the spinal cord (Tanji and Hoshi, 2008). Dorsal premotor cortex is involved in the integration of sensory and task information during action preparation and execution (Dum and Strick, 1991, Hoshi, 2006, Hoshi and Tanji, 2007). TMS and tDCS data indicate that prefrontal cortex is functionally linked to motor networks, wherein stimulation of prefrontal cortex modulates cortical spinal excitability depending on the nature and cognitive control demands of the task (Hasan et al., 2013; Tunovic et al., 2014; Vaseghi et al., 2015a; b). Evidence from this thesis (Chapter 6) supports the suggestion that prefrontal tDCS modulates corticospinal excitability, possibly though premotor-motor cortex connections (Vaseghi et al., 2015a). Because the effects of prefrontal tDCS on corticospinal excitability and dual-task gait were related (Chapter 7) and prefrontal tDCS appears to influence motor network activity in a task dependent manner (Chapter 6) the results of this thesis suggest that prefrontal cortex/FPN may mediate behaviour through alterations in corticospinal activity.

Further support for a guided activation model for prefrontal cortex control of dual task gait can be found in the role of dual-task prioritisation on prefrontal tDCS. The guided activation theory suggests that prefrontal cortex bias of ongoing neural processes is influenced by the relative strengths of competing goal related responses. Speculatively, if a role of prefrontal cortex/FPN is to bias task processing based on relevant task goals, one might assume that in dual-task performance the effects of prefrontal tDCS would be mediated by individual-task prioritisation strategies.

Yogev-Seligmann et al.'s (2012) model of task prioritization suggests that during dual-task gait, individuals selectively prioritise either cognitive or walking task performance. Individual prioritisation strategies are influenced by both physiological and cognitive capacity and by environmental constraints. Early evidence for inter-individual variation in prioritisation strategies was provided by Yogev-Seligmann *et* *al.*, (2010) who examined the effect of prioritisation instructions on dual-task gait speed. Yogev-Seligmann et al., (2010) reported that both young and old adults increased dual-task gait speed when asked to prioritise gait over cognitive task performance, compared to when they were given no explicit prioritisation instructions. Dual-task gait performance thus appeared to be mediated by the priority an individual gives to performance of each task. Subsequently, Kelly and colleagues (Kelly et al., 2010, 2013) reported that younger adults shifted task prioritization depending on both task instructions and the difficulty of the walking task.

In Chapters 4 and 5, STV was lower during dual-task gait than single task gait, regardless of changes to walking speed or cognitive task type. The magnitude of STV is assumed to represent the automaticity or the extent of cognitive control of dual-task gait and increases and decreases in STV are interpreted as changes to the cognitive control of gait (Montero-Odasso et al., 2012; Gabell and Nayak, 1984). Therefore, the results of Chapters 4 and 5 indicate that during treadmill walking, participants allocated cognitive control resources away from gait, toward cognitive task performance. In Chapter 7, treadmill walking again reduced STV. However, STV was higher during over-ground dual-task than during single task walking, and there was a walking modality dependent effect of tDCS on dual-task gait. Thus, cognitive control priorities during dual-task gait appear to be dependent on walking modality. These findings are in accordance with reports that changes in task prioritisation occur when the constraints of the walking task are changed (Kelly et al., 2010, 2013).

There is emerging evidence that prefrontal cortex is involved in task prioritisation during dual-task gait. Hobert et al., (2011) reported an association between task prioritisation and prefrontal dependent executive function in older adults. In their study, adults who performed poorly in the trail making executive function test, which activates prefrontal cortex (Zakzanis et al., 2005), prioritised cognitive task performance over gait performance. Subsequently, Takeuchi et al., (2016) have reported that young and old adults display altered prefrontal cortex activation during dual-task gait performance and this was related to differences in task prioritisation between the two groups. Because in Chapter 7 dual-task prioritisation and the effects of prefrontal tDCS on dual-task gait were different across walking modalities, the results of this thesis add to the literature indicating prefrontal cortex may be involved in task prioritisation during dual-task gait.

Kelly *et al.*, (2010; 2013) suggested that the difficulty of the walking task influences healthy adults' dual-task prioritisation strategies. However, the results of this thesis do not support their suggestion. In Chapter 4, participants found performing serial subtractions more difficult when walking slowly than when walking at their preferred speed. However, STV was reduced at both walking speeds during dual-task walking. In contrast, in Chapter 7 there was no difference in perceived difficulty between the two walking modalities but task prioritisation strategies were markedly different. Therefore, factors other than the relative difficulty of each task must influence task prioritisation. The reasons why individuals may prioritise different aspects of dual-task walking, resulting in differences in the allocation of cognitive control (and prefrontal cortex activity), remains unclear. We were unable to examine the difference in task coordination between over-ground and treadmill walking in Chapter 7, but it remains a possibility that differences in coordination between walking and cognitive tasks underlie these differences. Alternatively, integration of visual information during over-ground walking may place increased demands on cognitive control systems. Humans utilise optic flow to control gait (Gibson, 1958; Warren et al., 2001) and FPN is involved in processing optic flow (Merchant et al., 2003). Optic flow, or the perception thereof, appears to differ between treadmill and over-ground walking (Sheik-Nainar and Kaber, 2007) and may thus influence both cognitive control strategies, and prefrontal cortex/FPN activity.

In summary, the results of this thesis indicate that prefrontal cortex bias of neural processes during dual-task gait, indicated here by changes in walking performance, may be dependent on the relative priority of each task. These findings are in accordance with the guided activation theory of prefrontal cortex function (Miller and Cohen, 2001) which posits that prefrontal cortex biases ongoing neural processes depending on the relative strengths of each competing process. They are also in accordance with the theory of dual-task prioritization (Yogev- Seligmann et al., 2012) which states that performance in both tasks during dual-task performance is dependent on the relative priority of each task, itself influenced by possible challenges to postural stability, represented here by different walking modalities.

8.3.2 The Use of Transcranial Direct Current Stimulation to Examine the Neural Correlates of Gait Control

Since the seminal studies of Nitsche and Paulus at the beginning of the 21st century (Nitsche and Paulus, 2000, 2001), a growing body of research has examined the efficacy of tDCS to modulate brain activity and alter behaviour. Early studies of the physiological effects of motor cortex tDCS on cortical excitability reported a polarity dependent effect of tDCS, where anodal tDCS was reported to increase, and cathodal decrease, cortical excitability through alterations in cellular membrane potential. Application of tDCS for over 10 minutes was suggested to lead to Hebbian alterations in synaptic function (Nitsche and Paulus, 2000, 2001, Nitsche et al., 2003b, 2004). Early examinations of the effect of tDCS on cognitive function, building from these pioneering studies, reported that prefrontal tDCS also elicited a polarity dependent effect on cognitive function, analogous to the effects of motor cortex tDCS on cortical excitability (Fregni et al., 2005; Boggio et al., 2006; Fecteau et al., 2007; Teo et al., 2011; Zaehle et al., 2011). Subsequently however, a number of researchers suggested that the dichotomous ‘anodal excites\cathodal inhibits’ description of the effects of tDCS on cognition may be too simplistic. Systematic reviews on the effects of tDCS in both motor and cognitive domains revealed that the effects of tDCS on cognition do not reliably follow the canonical polarity dependent excitability\inhibition dichotomy (Jacobson et al., 2012; Horvath et al., 2014b, 2015). Indeed, both facilitative and inhibitive effects on cognition have been reported following anodal and cathodal tDCS (Monti et al., 2008; Marshall et al., 2005; Weiss and Lavidor, 2012; Filmer et al., 2013). Perhaps most damning of all, high inter-individual variability in changes to motor cortex excitability after tDCS have now been reported (López-Alonso et al., 2014, 2015; Wiethoff et al., 2014). Given the variation in physiological effects of tDCS, it seems highly unlikely that reliable, polarity dependent, effects on cognition should be expected (Horvath et al., 2015).

The results of this thesis replicate previous reports of high inter-individual variability in response to tDCS. The results of Chapter 5 revealed a polarity dependent effect of tDCS on treadmill dual-task gait, where anodal tDCS reduced, and cathodal tDCS appeared to increase the dual-task cost on STV. However, these results were not replicated in Chapter 7, where there was no effect of tDCS on treadmill dual-task. A number of research groups have also reported effects of tDCS on working memory performance (Fregni et al., 2005; Hoy et al., 2013; Zaehle et al., 2011). However, in Chapter 6, there was no improvement in working memory performance following stimulation.

The causes of variability in the effects of tDCS are still not fully understood. A broad range of anatomical and physiological factors have been suggested to influence stimulation. These include variations in genotype (Nieratschker et al., 2015) cranial and brain anatomy (Bikson et al., 2012), neurotransmitter balance (Krause et al., 2014) amongst others (see Li et al., (2015) and Datta et al., (2012) for a review). The effects of tDCS also appear to be dependent on task specific physiological and behavioural factors. Tseng et al., (2012), Benwell *et al.*, (2015) and Learmonth et al., (2015) reported that the effects of tDCS were at least partially dependent on inter-individual baseline task performance characteristics. These data highlight the state dependency of stimulation effects, where non-linear effects of stimulation occur in response to the underlying activity of the stimulated neuronal structures (Bestmann et al., 2014).

Alternatives to the excitation/inhibition model for tDCS effects include the zero sum and stochastic resonance models. The zero sum model of tDCS, itself derived from game theory, suggests that the brain is a closed system with a finite energy supply and processing resources. Under the zero-sum model, because there is a finite pool of processing resources, enhancements or ‘gains’ to specific brain functions must also result in costs or ‘losses’ in different processes or structures (Brem et al., 2014). Alternatively, the stochastic resonance model is based on the assumption that biological systems have a measurement threshold, which is altered by the signal to noise ratio of the given input (Stocks, 2000). The performance of such a system requires the comparison between the response to noise to the response to noise plus signal (Miniussi et al., 2013). If the signal strength is below the measurement threshold, injection of low levels of noise, for example from tDCS, facilitate the detection the signal by increasing the input strength to past the detection threshold. Conversely, if the signal strength is at or above the detection threshold, injection of noise can impair signal detection because of the alteration in the noise to signal-plus-noise comparison (Miniussi et al., 2013). The results of this thesis can partially be explained using these two frameworks.

In Chapter 5, prefrontal anodal tDCS altered the allocation of cognitive control across walking and cognitive tasks during dual-task gait. This finding could be considered analogous with the zero-sum model for tDCS effects, whereby an improvement in one task leads to a cost in another (Brem et al., 2014). Because tDCS appeared to alter the allocation of cognitive control from gait to cognitive task performance, it may be the case that prefrontal tDCS lead to improvements cognitive task performance only at a cost to walking performance. However, there are several issues with this interpretation. Firstly, it is unclear whether the brain can truly be considered a closed, finitely resourced, system (Luber, 2014). Additionally, under the dual-task gait paradigm, alterations in the allocation of cognitive control toward or away from gait do not necessarily represent improvements or reductions in gait performance. Both low and high STV are linked to increased fall risk (Beauchet et al., 2009a), likely because the locomotive system requires a degree of variability and thus possibly cognitive control, to function (Dingwell et al., 2010; Beauchet et al., 2009a). It is perhaps more accurate to describe these effects simply as *changes* in dual-task gait performance, with the benefit, or not, of these changes remaining unclear. Despite these reservations, the zero-sum concept provides a useful framework against which the results of Chapter 5 can be interpreted.

The stochastic resonance model (Miniussi et al., 2013) addresses the apparent state dependent nature of stimulation; the noise to signal ratio, and the detection thereof, is itself mediated by the underlying state of neuronal populations involved in signal detection. The injection of noise into a system would thus only enhance signal detection if the noise-plus-signal resulted in the signal reaching a detection threshold. If the input strength already exceeds the detection threshold, then an injection of additional noise, such as tDCS, may impair signal detection (Miniussi et al., 2013). The disparity between the effects of offline and online tDCS on treadmill based dual-task gait can be interpreted using the stochastic resonance model. In Chapter 5, offline stimulation may have increased input signal strength toward the detection threshold, resulting in changes in behaviour. Conversely, online stimulation (during gait in Chapter 7) may have resulted in excessive input strength, because the control of locomotion increases neural processing (Holtzer et al., 2014). Therefore, the disparity between the effects of tDCS on treadmill dual-task gait between Chapters 5 and 7 may be due to the differences in stimulation type (online vs offline) and the resultant alterations in the signal/noise ratio that occurs during gait. Whilst the alteration in over-ground dual-task walking in Chapter 7 might be interpreted as evidence against a stochastic resonance explanation of these results, these effects were themselves dependent on the perceived task difficulty, a surrogate marker of neural ‘state’.

A number of authors have suggested that non-linear effects of tDCS are due to the underlying state of the neural networks utilised during the cognitive task. This is seen through the opposing effects of tDCS between those who find the task easiest and those who find it hardest (Benwell et al., 2015; Learmonth et al., 2015; Tseng et al., 2012). Cognitive task difficulty is suggested to indicate the underlying state of neural networks being activated (Benwell et al., 2015). Within the stochastic resonance framework, injections of neural noise into these systems would result in relative differences in input strength and thus differences in the ability to determine signal from noise. Therefore, in Chapter 7, the effect of perceived difficulty on stimulation effects may represent differences in the underlying state of neuronal populations. The implications of these findings is that both baseline performance characteristics and measures of perceived effort need to be controlled for when examining the effects of tDCS on whole body actions, such as gait.

At first glance support for both of these models results may seem counter intuitive; the zero –sum model suggests a sliding scale effect of tDCS, where there are clear polarity dependent effects (both gains and losses) following stimulation. In contrast, the stochastic resonance model suggests that a uniform polarity dependent effect of stimulation is not possible, and instead inter and intra individual variation in the state of the brain tissue would mediate stimulation effects. However, these models are by no means definitive description of tDCS effects, and simply provide post-hoc explanations of reported effects (Bestmann et al., 2014). More sophisticated systems wide models are required in order to correctly interpret, and predict tDCS effect (Bestmann et al., 2014). Nonetheless, they allow a more nuanced interpretation of the effects of prefrontal tDCS on dual-task performance than simplistic polarity dependent improvements in “performance”. Both models highlight that the capacity for tDCS to elicit changes in performance is not uniform across individuals, and there is a clear need to identify methods by which individual responses to tDCS can be predicted for it to be reliably used to examine, and improve, cognitive functions (Filmer et al., 2014; Tremblay et al., 2014; Horvath et al., 2015).

8.3.3 The Relationship between the Effects of Prefrontal tDCS on Cognitive and Corticospinal Excitability

In Chapter 6, prefrontal tDCS modulated corticospinal excitability. These findings replicate previous reports of altered corticospinal excitability following prefrontal tDCS (Vaseghi et al., 2015a; b). In addition, in Chapter 7, for the first time, we have shown that the effects of prefrontal tDCS on dual-task gait is related to its effects on corticospinal excitability. Bortoletto et al., (2015) reported a significant correlation between the effects of motor cortex tDCS on corticospinal excitability and motor learning in a finger movement task. Their results indicated that the effects of motor cortex tDCS on behaviour are related to its effects on corticospinal excitability. Because stimulation of prefrontal cortex modulates corticospinal excitability (Chapter 6), in Chapter 7, we examined whether the effects of anodal prefrontal tDCS on dual-task gait and corticospinal excitability were also related. Results revealed that tDCS effects on corticospinal excitability and dual-task gait were negatively correlated during treadmill, but not over-ground, walking.

Prefrontal cortex is functionally connected to, and modulates the activity of, motor networks which include motor cortex and the corticospinal tract (Hoshi, 2006; Tanji and Hoshi, 2008). As highlighted previously, the results of this thesis indicate that prefrontal cortex may influence the cognitive control of gait through modulation of these networks. There is also emerging evidence that the effects of motor cortex tDCS on corticospinal excitability are dependent on I-Wave recruitment during TMS (Wiethoff et al., 2014; McCambridge et al., 2015; Davidson et al., 2016). I-waves are thought to originate from mono and polysynaptic inputs to pyramidal tract neurons (Di Lazzaro et al., 2012) and are modulated by the dorsal premotor cortex (Volz et al., 2015). It is tempting to speculate that the relationship between the effects of prefrontal tDCS on behaviour and physiology reported within this thesis represent the influence of prefrontal cortex, through the premotor cortex, on I-wave recruitment. However, this interpretation must be approached with caution, there is little direct evidence of alterations in I-wave recruitment from prefrontal stimulation, and the relationships reported here are moderate and in small sample sizes.

Nonetheless, this is an area which deserves further examination, and may provide valuable insight into the nature of the influence of prefrontal cortex on motor networks. Alternatively, the correlation seen in the present thesis and elsewhere (Bortoletto et al., 2015) may also represent the influences of physiological and anatomical factors on tDCS effects. Various physiological and anatomical factors, including sub-cutaneous fat levels, skull thickness and brain structure have all been suggested to influence tDCS effects (Opitz et al., 2015; Truong et al., 2013). Speculatively, the relationships reported between physiological and behavioural changes after tDCS reported here and elsewhere (Bortoletto et al., 2015) may represent the influence of these mediators on stimulation effects.

Although these results provide a possible mechanism by which the behavioural effects of prefrontal tDCS may be predicted, they must also be interpreted with some caution. The correlation between behavioural and physiological tDCS effects within this thesis was only moderate, and in a small sample size. It therefore requires replication in a larger population. Additionally, whilst there may be a relationship between physiological and behavioural effects of prefrontal tDCS, it is not clear what this relationship represents. Further examination of the nature of prefrontal cortex to motor cortex connections, and the effects of stimulation on motor network activity, is required to further understanding of the mechanisms underpinning this relationship.

8.4. Applications of the Thesis

Prefrontal cortex volume reduces with age, and this has been linked to changes in gait performance (Dickstein et al., 2007; Rosano et al., 2012). Dual-task gait performance also decreases with age, and is linked to increased fall risk (Beauchet et al., 2009b). Whilst older adults activate prefrontal cortex during dual-task gait, they appear to do so less than younger adults (Holtzer et al., 2011). Older adults also do not alter neural activation patterns to the same extent as younger adult during dual-task gait, possibly due to reduced ‘neural flexibility’ (Malcolm et al., 2015). The results from this thesis may help to explain the relationship between old age, dual-task performance and fall risk. The results of this thesis indicate that prefrontal cortex is involved in the flexible allocation of cognitive resources during dual-task gait. Age related reduction in prefrontal cortex structure and function would thus be expected to reduce the ability to flexibly allocate cognitive resources during dual-task walking, which would impair both hazard perception and response (Yogev-Seligmann et al., 2012). Whether neural flexibility during dual-task gait performance is entirely dependent on prefrontal cortex function remains to be investigated. Nonetheless, research examining the efficacy of therapies to target this processes, and the resultant effect on dual-task gait performance, is warranted. Intriguingly, reductions in older adults' cognitive flexibility has also been linked to improper task prioritisation during dual-task gait (Hobert et al., 2011). Cognitive flexibility has been identified as a prefrontal cortex dependent executive function (Miyake et al., 2000; Diamond, 2013). Whether cognitive flexibility is synonymous with neural flexibility is unclear. Examination of the relationship between these two factors, and dual-task gat performance, may improve understanding of the nature of prefrontal cortex mediated dual-task gait dysfunction in older adults.

Improving cognitive function through cognitive-motor training, such as dual-task gait, has been proposed as a possible therapy to improve gait performance and reduce fall risk in older adults (Montero-Odasso et al., 2012). Verghese et al., (2010) reported that cognitive training reduced the dual-task cost on gait speed. Others have reported that dual-task gait training also reduces the dual-task cost on gait (Silsupadol et al., 2009; Schwenk et al., 2010). However, at present there is little evidence that cognitive-motor training interventions, such as virtual reality or exergaming programmes, are more effective at reducing fall risk than usual rehabilitation (Schoene et al., 2014). This may be due to the heterogeneity of intervention types examined (Schoene et al., 2014). Alternatively, it may be because the prevalent model of the cognitive control of gait, and dual-task gait in particular, is poorly understood. Prominent dual-task gait models (e.g. Yogev-Seligmann et al., 2008), link executive function, attention and prefrontal cortex but do not describe the nature of that relationship. The results of this thesis, in accordance with evidence from neural network analysis (Cole et al., 2013; Malcolm et al., 2015; Alavash et al., 2015; Cole et al., 2015), indicate that prefrontal cortex/FPN appears to be involved in the flexible allocation and adaptation of cognitive control processes during dual-task gait. Therefore, future studies examining the effect of cognitive-motor therapies on the cognitive control of gait should examine their effects on prefrontal cortex-mediated neural/cognitive flexibility. Targeting specific neural/cognitive processes which are likely to be involved in the control of dual-task gait may result in discovery of more effective therapies to combat fall risk in older adults.

There is a large and growing body of work reporting beneficial effects of tDCS on cognitive and physical function, including dual-task gait (Kuo and Nitsche, 2012; Schulz et al., 2012; Manor et al., 2016; Zhou et al., 2014). tDCS is also suggested to be a promising method to examine neural correlates of behaviour (Filmer et al., 2014). However, the results of this thesis add to the growing body of literature reporting large inter-individual response to tDCS and reveal that the effects of tDCS on dual-task gait performance also exhibit large inter-individual variation (Wiethoff et al., 2014; Tremblay et al., 2014). Whether tDCS can reliably be used to alter behaviour is a widely debated, and controversial, issue (Horvath et al., 2015, 2014b; Antal et al., 2015; Chhatbar and Feng, 2015). The results of this thesis reveal that physiological and behavioural effects of tDCS vary between individuals (Chapter 5, 6, and 7) and can be explained by contrasting existing theories of tDCS effects. The results of the present thesis, in support of recent reports of tDCS variability (Wiethoff et al., 2014; Davidson et al., 2016) suggest that it is unlikely that tDCS will uniformly “improve” any cognitive or cognitive-motor behaviour, and so reports of tDCS induced improvements in behaviour must be approached with some caution. Therefore, there is a clear need for improved models of tDCS function, so that the cause of individual differences in response can be predicted. The results of Chapter 6 and 7 indicate that the behavioural effects of prefrontal tDCS may be related to changes in corticospinal excitability. Whilst these data require replication is a much larger sample, and the underlying mechanisms revealed, this finding offers a possible avenue to further understanding of the effects of, and possibilities for, prefrontal tDCS.

8.5. Directions for Future Research

The experimental results of this thesis have generated a number of possible avenues for future research, outlined below.

8.5.1 The Role of Prefrontal Cortex in Task Prioritisation during Dual-Task Performance

The results of the present thesis, in accordance with prominent theories of prefrontal cortex function (Miller, 2000; Miller and Cohen, 2001), suggest that prefrontal cortex is involved in task prioritisation during dual-task gait performance. Within the dual-task gait literature, two different task prioritization strategies have been identified: posture first, and posture second. Adoption of a posture first strategy results in the individual prioritising gait and balance during dual-task walking (Shumway-Cook et al., 1997). Conversely, posture second strategy would mean the individual prioritises cognitive task performance over gait Early models of task prioritisation suggested that healthy adults' would naturally adopt a posture first strategy unless given explicit instructions (Shumway-Cook et al., 1997). Conversely neurological patients, such as those with Parkinson's disease, were suggested to (inappropriately) adopt a posture second strategy, increasing fall risk (Bloem et al., 2006). Subsequent experimental and theoretical accounts of task prioritisation during dual-task walking have identified a range of physiological and psychological factors which influence task prioritisation strategies, including environmental and walking conditions, explicit prioritisation instructions and individual executive capacity (Kelly et al., 2010; Yogev-Seligmann et al., 2010; Yogev- Seligmann et al., 2012). Because inappropriate task prioritisation strategies may result in gait dysfunction and increased fall risk, there is a clear need to understand the mechanisms underpinning task prioritisation during dual-task gait.

The results of Chapter 5 and 7 indicate that prefrontal cortex bias of task performance may be dependent on task prioritisation strategies during dual-task gait, and evidence from elsewhere suggests that task prioritisation is influenced by the capacity of prefrontal cortex dependent executive functions (Hobert et al., 2011; Yogev- Seligmann et al., 2012). Prefrontal cortex degeneration and cognitive impairment are linked to a reduced gait performance and increased fall risk (Rosano et al., 2012; Liu-Ambrose et al., 2008). The results of this thesis indicate that prefrontal cortex may alter task prioritisation during dual-task gait, which in turn may increase fall risk (Bloem et al., 2006). However, one limitation of the current thesis is that the effects of tDCS on explicit priorities strategies was not investigated. Healthy adults will alter task prioritisation strategies when given explicit instructions to do so (Kelly et al., 2010; Yogev-Seligmann et al., 2010). Examination of the effects of prefrontal tDCS on dual-task performance with and without explicit task prioritisation instructions would enable researchers to have a deeper understanding of the role of prefrontal cortex in task prioritisation during dual-task gait.

8.5.2 State Dependency in tDCS Effects on Dual-Task Gait

Current models of tDCS indicate that stimulation effects are dependent on the state of neuronal populations being stimulated, both under the electrode and in functionally and anatomically connected areas and networks (Miniussi et al., 2013; Bestmann et al., 2014). Recent controversy over the effects of tDCS and their reliability makes use of the technique to examine and modify cognitive-motor processes difficult (Tremblay et al., 2014; Horvath et al., 2015). There is therefore a clear need to understand which factors influence the behavioural consequences of stimulation (Bestmann et al., 2014)

In Chapter 5, offline anodal prefrontal tDCS reduced the dual-task cost on STV and cognitive task performance, indicating an alteration in task processing. In Chapter 7, however, online tDCS did not alter treadmill dual-task gait performance and its effects on over-ground dual task walking were themselves mediated by individual perceptions of task difficulty. Comparison of online and offline prefrontal stimulation protocols have revealed differential effects depending on timing and the age of population (Wirth et al., 2011; Fertonani et al., 2014). Therefore, these results may be explained by the differences in neuronal states between online and offline stimulation, and between those who find the task hardest and those who find it easier (Miniussi et al., 2013; Benwell et al., 2015). However, the effects of online and offline stimulation on dual-task gait performance were not directly compared in this thesis. Within the tDCS literature, individual variation in task performance is suggested to indicate the magnitude of neural processing required to perform the task, which under the stochastic resonance framework would then mediate tDCS effects on behaviour (Tseng et al., 2012; Benwell et al., 2015; Learmonth et al., 2015). In Chapter 7, we extended these results top show that perceived difficulty also influenced tDCS. However, neither within this thesis, nor within the general tDCS literature, has the effect on task difficulty on tDCS been quantifiably linked to the state of the targeted neural structures.

There is therefore a need to understand whether stimulation timing mediates tDCS effects on dual-task gait. Because perceived task difficulty influenced the effects of tDCS on over-ground dual-task gait, it is also important to understand both the relationship between perceived difficulty and neuronal state, and the influence of perceived difficulty on both online and offline stimulation protocols. Comparison of the effects of offline and online stimulation on dual-task gait, and the influence of task performance and perceived difficulty on those effects, would improve understanding not only of possible mediators of tDCS effects, but of the nature of prefrontal cortex activation during dual-task walking.

8.5.3 Probing the Mechanisms by Which Prefrontal Cortex Modulates Corticospinal Excitability

In Chapter 6, cathodal prefrontal tDCS reduced corticospinal excitability. A reduction in corticospinal excitability following cathodal prefrontal tDCS was also reported by Vaseghi et al., (2015a). Cathodal tDCS may reduce cortical excitability (Nitsche and Paulus, 2000), suggesting that a reduction of prefrontal cortex activity may reduce corticospinal excitability. Tunovic et al (2014) delivered theta-burst TMS to prefrontal cortex, wherein stimulation can be either continuous or intermediate, immediately after a motor learning task and reported that stimulation of prefrontal cortex also influenced corticospinal excitability. When applied to motor cortex, continuous theta burst TMS decreases, whilst intermediate stimulation increases corticospinal excitability (Huang et al., 2005). In contrast Tunovic et al reported that intermediate theta burst TMS applied to prefrontal cortex reduced corticospinal excitability. Hasan et al., (2013) used TMS to probe prefrontal cortex connections to the corticospinal system, and reported that prefrontal cortex exerts task and timing specific influences on the corticospinal system, whereby task and timing relevant visual cues differentially increased and decreased corticospinal excitability. Taken together, these findings indicate that prefrontal cortex exerts a functional influence on the corticospinal system, including motor cortex.

Connectivity between prefrontal cortex and the corticospinal system can be probed using twin coil TMS whereby a pulse is initially delivered to prefrontal cortex and then subsequently to motor cortex during a motor action (Hasan et al., 2013). Hasan and colleagues found that manipulation of the inter-stimulus interval influenced prefrontal cortex-corticospinal connectivity, indicating that prefrontal cortex modulation of corticospinal was bound to the temporal dynamics of the action. Recent work using TMS and EEG in combination has allowed researchers to examine the effects of stimulation on cortical excitability in areas up and downstream of motor cortex (Aron et al., 2016). Paired pulse TMS, where motor cortex is stimulated twice, both below and above motor threshold. Altering the inter-stimulus interval facilitates or inhibits MEP amplitude, reflecting inhibitive and facilitative inter-neuronal influences on motor cortex excitability (Ziemann et al., 1996). Probing the nature of tDCS modulation of prefrontal cortex-corticospinal connectivity using these techniques would reveal the nature both functional connectivity between prefrontal and motor networks, and the effects of tDCS on them.

8.6. Conclusion

In conclusion, the results of the present thesis support previous imaging (Holtzer et al., 2011) and tDCS (Zhou et al., 2014) evidence linking prefrontal cortex to the control of dual-task gait. This thesis has extended these results to show that prefrontal tDCS alters the allocation of cognitive resources across both tasks during dual-task walking, highlighting the possible role of prefrontal cortex in the bias of neural processing across task relevant networks (Chapter 2 and 4, Miller & Cohen, 2001). Because the effects of prefrontal tDCS on dual-task gait are mediated by walking modality and task difficulty, these results provide provisional data indicating that the effects of tDCS on dual-task gait are influenced by the relative priority of each task, suggesting that prefrontal cortex bias of neural processes during dual-task performance may reflect task prioritisation strategies. In Chapters 3 and 4, the effects of prefrontal tDCS on corticospinal excitability were related to changes in cognitive and dual-task performance. These results indicate that during dual-task gait, prefrontal cortex influences the activity in motor networks based to task goals and priorities, in accordance with prominent theories of the role prefrontal cortex in cognitive control (Miller and Cohen, 2001; Cole and Schneider, 2007).

9. References

Abernethy, B., 1988. Dual-task methodology and motor skills research: Some applications and methodological constraints. *Journal of Human Movement Studies*, 14(3), pp.101–132.

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K. and Cockburn, J., 2011. Cognitive motor interference while walking: a systematic review and meta-analysis. *Neuroscience and biobehavioral reviews*, 35(3), pp.715–28.

Alamgir, H., Muazzam, S. and Nasrullah, M., 2012. Unintentional falls mortality among elderly in the United States: time for action. *Injury*, 43(12), pp.2065–71.

Alavash, M., Hilgetag, C.C., Thiel, C.M. and Gießing, C., 2015. Persistency and flexibility of complex brain networks underlie dual-task interference. *Human Brain Mapping*, 36(9), pp.3542–3562.

Allali, G., Assal, F., Kressig, R.W., Dubost, V., Herrmann, F.R. and Beauchet, O., 2008. Impact of impaired executive function on gait stability. *Dementia and geriatric cognitive disorders*, 26(4), pp.364–9.

Allali, G., Dubois, B., Assal, F., Lallart, E., de Souza, L.C., Bertoux, M., Annweiler, C., Herrmann, F.R., Levy, R. and Beauchet, O., 2010. Frontotemporal dementia: pathology of gait? *Movement disorders*, 25(6), pp.731–7.

Allali, G., Kressig, R.W., Assal, F., Herrmann, F.R., Dubost, V. and Beauchet, O., 2007. Changes in gait while backward counting in demented older adults with frontal lobe dysfunction. *Gait & posture*, 26(4), pp.572–6.

Amazeen, P.G., Amazeen, E.L. and Beek, P.J., 2001. Coupling of breathing and movement during manual wheelchair propulsion. *Journal of experimental psychology. Human perception and performance*, 27(5), pp.1243–1259.

American Geriatrics Society, 2001. Guideline for the Prevention of Falls in Older Persons. *Journal of the american geriatrics society*, 49(5), pp.664–672.

Aminian, K., Najafi, B., Büla, C., Leyvraz, P.-F. and Robert, P., 2002. Spatio-temporal parameters of gait measured by an ambulatory system using miniature gyroscopes. *Journal of Biomechanics*, 35(5), pp.689–699.

Aminian, K., Trevisan, C., Najafi, B., Dejnabadi, H., Frigo, C., Pavan, E., Telonio, A., Cerati, F., Marinoni, E.C., Robert, P. and Leyvraz, P.-F., 2004. Evaluation of an ambulatory system for gait analysis in hip osteoarthritis and after total hip replacement. *Gait & posture*, 20(1), pp.102–7.

Andrés, P., 2003. Frontal Cortex as the Central Executive of Working Memory: Time to Revise Our View. *Cortex*, 39(4), pp.871–895.

Andrés, P. and Linden, M. Van Der, 2002. Are central executive functions working in patients with focal frontal lesions? *Neuropsychologia*, 40(7), pp.835–845.

Aniss, A.M., Gandevia, S.C. and Burke, D., 1992. Reflex responses in active muscles elicited by stimulation of low-threshold afferents from the human foot. *Journal of neurophysiology*, 67(5), pp.1375–84.

Antal, A., Keeser, D., Priori, A., Padberg, F. and Nitsche, M. a., 2015. Conceptual and procedural shortcomings of the systematic review "Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic r. *Brain stimulation*, 8, pp.846–849.

Armieri, A., Holmes, J. and Spaulding, S., 2009. Dual task performance in a healthy young adult population: Results from a symmetric manipulation of task complexity and articulation. *Gait & posture*, 29(2), pp.346–348.

Armstrong, D.M., 1988. The supraspinal control of mammalian locomotion. *The Journal of physiology*, 405, pp.1–37.

Aron, A., Nigel, T.H., Paul, C.R. and Hoy, K.E., 2016. TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. *Neuroscience and biobehavioral reviews*, 64, pp.175–184.

Asai, T., Doi, T., Hirata, S. and Ando, H., 2013. Dual tasking affects lateral trunk control in healthy younger and older adults. *Gait & posture*, 38(4), pp.830–836.

Atkinson, G. and Nevill, A.M., 1998. Measurement Error (Reliability) in Variables

Relevant to Sports Medicine. *Sports Medicine*, 26(4), pp.217–238.

Atsumori, H., 2010. Noninvasive imaging of prefrontal activation during attention-demanding tasks performed while walking using a wearable optical topography system. *Journal of Biomedical Optics*, 15(4), p.46002.

Baddeley, A., 1996. Exploring the Central Executive. *The Quarterly Journal of Experimental Psychology A*, 49(1), pp.5–28.

Baddeley, A., 2000. The episodic buffer: a new component of working memory? *Trends in cognitive sciences*, 4(11), pp.417–423.

Baddeley, A., 2003. Working memory: looking back and looking forward. *Nature reviews neuroscience*, 4(10), pp.829–39.

Baddeley, A. and Hitch, G., 1994. Developments in the concept of working memory. *Neuropsychology*, 8(4), p.485.

Baddeley, A., Della Sala, S., Papagno, C. and Spinnler, H., 1997. Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion. *Neuropsychology*, 11(2), pp.187–94.

Barker, A.T., Jalinous, R. and Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. *Lancet*, 1(8437), pp.1106–7.

Bastani, A. and Jaberzadeh, S., 2013. Differential modulation of corticospinal excitability by different current densities of anodal transcranial direct current stimulation. *PLoS ONE*, 8(8), p.e72254.

Beauchet, O., Allali, G., Annweiler, C., Bridenbaugh, S., Assal, F., Kressig, R.W. and Herrmann, F.R., 2009a. Gait variability among healthy adults: low and high stride-to-stride variability are both a reflection of gait stability. *Gerontology*, 55(6), pp.702–6.

Beauchet, O., Annweiler, C., Allali, G., Berrut, G., Herrmann, F.R. and Dubost, V., 2008. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? *Journal of the american geriatrics society*, 56(7), pp.1265–9.

Beauchet, O., Annweiler, C., Dubost, V., Allali, G., Kressig, R.W., Bridenbaugh, S., Berrut, G., Assal, F. and Herrmann, F.R., 2009b. Stops walking when talking: a predictor of falls in older adults? *European journal of neurology*, 16(7), pp.786–95.

Beauchet, O., Annweiler, C., Lecordroch, Y., Allali, G., Dubost, V., Herrmann, F.R. and Kressig, R.W., 2009c. Walking speed-related changes in stride time variability: effects of decreased speed. *Journal of neuroengineering and rehabilitation*, 6, p.32.

Beauchet, O., Annweiler, C., Montero-Odasso, M., Fantino, B., Herrmann, F.R. and Allali, G., 2012. Gait control: a specific subdomain of executive function? *Journal of neuroengineering and rehabilitation*, 9(1), p.12.

Beauchet, O., Dubost, V., Aminian, K., Gonthier, R. and Kressig, R.W., 2005a. Dual-task-related gait changes in the elderly: does the type of cognitive task matter? *Journal of motor behavior*, 37(4), pp.259–264.

Beauchet, O., Dubost, V., Herrmann, F.R. and Kressig, R.W., 2005b. Stride-to-stride variability while backward counting among healthy young adults. *Journal of neuroengineering and rehabilitation*, 2, p.26.

Beauchet, O., Kressig, R.W., Najafi, B., Aminian, K., Dubost, V. and Mourey, F., 2003. Age-related decline of gait control under a dual-task condition. *Journal of the american geriatrics society*, 51(8), pp.1187–1188.

Benarroch, E.E., 2013. Pedunculopontine nucleus: functional organization and clinical implications. *Neurology*, 80(12), pp.1148–55.

Benwell, C.S.Y.Y., Learmonth, G., Miniussi, C., Harvey, M. and Thut, G., 2015. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*, 69, pp.152–165.

Berryhill, M.E. and Jones, K.T., 2012. tDCS selectively improves working memory in older adults with more education. *Neuroscience letters*, 521(2), pp.148–151.

Bestmann, S., de Berker, A.O. and Bonaiuto, J., 2014. Understanding the behavioural consequences of noninvasive brain stimulation. *Trends in cognitive sciences*, pp.1–8.

Beurskens, R. and Bock, O., 2012. Age-related deficits of dual-task walking: a review. *Neural plasticity*, 2012, p.131608.

Beurskens, R., Helmich, I., Rein, R. and Bock, O., 2014. Age-related changes in prefrontal activity during walking in dual-task situations: a fNIRS study. *International journal of psychophysiology*, 92(3), pp.122–8.

Bikson, M., Rahman, A. and Datta, A., 2012. Computational Models of Transcranial Direct Current Stimulation. *Clinical EEG and Neuroscience*, 43(3), pp.176–183.

Bilney, B., Morris, M. and Webster, K., 2003. Concurrent related validity of the GAITRite® walkway system for quantification of the spatial and temporal parameters of gait. *Gait & posture*, 17(1), pp.68–74.

Bindman, L.J., Lippold, O.C.J. and Redfearn, J.W.T., 1964. The action of brief depolarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *Journal of physiology*, 172(3), pp.369–382.

Bloem, B.R., Grimbergen, Y.A.M., van Dijk, J.G. and Munneke, M., 2006. The ‘posture second’ strategy: a review of wrong priorities in Parkinson’s disease. *Journal of the neurological sciences*, 248(1–2), pp.196–204.

Bloem, B.R., Valkenburg, V. V, Slabbekoorn, M. and Willemsen, M.D., 2001. The Multiple Tasks Test. *Gait & posture*, 14(3), pp.191–202.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A. and Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson’s disease. *Journal of the neurological sciences*, 249(1), pp.31–38.

Bollens, B., Crevecoeur, F., Detrembleur, C., Warlop, T. and Lejeune, T.M., 2014. Variability of human gait: effect of backward walking and dual-tasking on the presence of long-range autocorrelations. *Annals of biomedical engineering*, 42(4), pp.742–50.

Borg, G., 1998. *Borg’s perceived exertion and pain scales.* Champaign, IL, USA: Human Kinetcis.

Boros, K., Poreisz, C., Münchau, A., Paulus, W. and Nitsche, M.A., 2008. Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. *The European journal of neuroscience*, 27(5), pp.1292–300.

Bortoletto, M., Pellicciari, M.C., Rodella, C. and Miniussi, C., 2015. The Interaction With Task-induced Activity is More Important Than Polarization: A tDCS Study. *Brain stimulation*, 8(2), pp.269–276.

Botvinick, M.M.M., Braver, T.S.T., Barch, D.D.M.D.D.M., Carter, C.S. and Cohen, J.D., 2001. Conflict monitoring and cognitive control. *Psychological Review*, 108(3), pp.624–652.

Bourke, P.A., Duncan, J. and Nimmo-Smith, I., 1996. A General Factor Involved in Dual task Performance Decrement. *The Quarterly Journal of Experimental Psychology A*, 49(3), pp.525–545.

Brach, J.S., Berlin, J.E., VanSwearingen, J.M., Newman, A.B. and Studenski, S. a, 2005. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. *Journal of neuroengineering and rehabilitation*, 2, p.21.

Brauer, S.G. and Morris, M.E., 2010. Can people with Parkinson’s disease improve dual tasking when walking? *Gait & posture*, 31(2), pp.229–33.

Braver, T.S., 2012. The variable nature of cognitive control: A dual-mechanisms framework. *Trends in cognitive sciences*, 16(2), pp.106–113.

Brem, A.-K.K., Fried, P.J., Horvath, J.C., Robertson, E.M. and Pascual-Leone, A., 2014. Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? *NeuroImage*, 85(3), pp.1058–1068.

Brown, L.A., McKenzie, N.C. and Doan, J.B., 2005. Age-Dependent Differences in the Attentional Demands of Obstacle Negotiation. *The journals of gerontology Series A: biological sciences and medical sciences*, 60(7), pp.924–927.

Brown, T.G., 1911. The Intrinsic Factors in the Act of Progression in the Mammal. *Proceedings of the Royal Society of London, Series B*, 84(572), pp.308–319.

Brown, T.G., 1914. On the fundamental activity of the nervous centres: together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *Journal of physiology*, 48(1), pp.18–46.

Calancie, B., 2006. Spinal myoclonus after spinal cord injury. *The journal of spinal* *cord medicine*, 29(4), pp.413–24.

Camicioli, R., Howieson, D., Lehman, S. and Kaye, J., 1997. Talking while walking: the effect of a dual task in aging and Alzheimer's disease. *Neurology*, 48, pp.955–958.

Capaday, C., Lavoie, B.A., Barbeau, H., Schneider, C. and Bonnard, M., 1999. Studies on the Corticospinal Control of Human Walking. I. Responses to Focal Transcranial Magnetic Stimulation of the Motor Cortex. *Journal of neurophysiology*, 81(1), pp.129–139.

Chhatbar, P.Y. and Feng, W., 2015. Data Synthesis in Meta-Analysis may Conclude Differently on Cognitive Effect From Transcranial Direct Current Stimulation. *Brain stimulation*, pp.3–5.

Chmielewski, W.X., Yildiz, A. and Beste, C., 2014. The neural architecture of age-related dual-task interferences. *Frontiers in aging neuroscience*, 6, p.193.

Civardi, C., Cantello, R., Asselman, P. and Rothwell, J.C., 2001. Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *NeuroImage*, 14(6), pp.1444–1453.

Cohen, A.H., Guan, L., Harris, J., Jung, R. and Kiemel, T., 1996. Interaction between the caudal brainstem and the lamprey central pattern generator for locomotion. *Neuroscience*, 74(4), pp.1161–1173.

Cohen, J.D., Aston-Jones, G. and Gilzenrat, M.S., 2004. A Systems-Level Perspective on Attention and Cognitive Control: Guided Activation, Adaptive Gating, Conflict Monitoring, and Exploitation versus Exploration. In: M. Posner, ed., *Cognitive neuroscience of attention*. New York: Guilford Press, pp.71–90.

Cole, M.W., Ito, T. and Braver, T.S., 2015. The Behavioral Relevance of Task Information in Human Prefrontal Cortex. *Cerebral Cortex*, 26(6), pp.2497–2505.

Cole, M.W., Pathak, S. and Schneider, W., 2010. Identifying the brains most globally connected regions. *NeuroImage*, 49(4), pp.3132–3148.

Cole, M.W., Reynolds, J.R., Power, J.D., Repovs, G., Anticevic, A. and Braver, T.S., 2013. Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature neuroscience*, 16(9), pp.1348–55.

Cole, M.W. and Schneider, W., 2007. The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, 37(1), pp.343–360.

Cole, M.W., Yarkoni, T., Repovs, G., Anticevic, A. and Braver, T.S., 2012. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *The Journal of neuroscience*, 32(26), pp.8988–99.

Collette, F., Olivier, L., Van der Linden, M., Laureys, S., Delfiore, G., Luxen, A. and Salmon, E., 2005. Involvement of both prefrontal and inferior parietal cortex in dual-task performance. *Cognitive brain research*, 24(2), pp.237–51.

Van de Crommert, H., Mulder, T. and Duysens, J., 1998. Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. *Gait & posture*, 7(3), pp.251–263.

Crossley, M., Hiscock, M. and Foreman, J.B., 2004. Dual-task performance in early stage dementia: differential effects for automatized and effortful processing. *Journal of clinical and experimental neuropsychology*, 26(3), pp.332–46.

D'Esposito, M., 2007. From cognitive to neural models of working memory. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 362(1481), pp.761–72.

D'Esposito, M., Detre, J.A., Alsop, D.C., Shin, R.K., Atlas, S. and Grossman, M., 1995. The neural basis of the central executive system of working memory. *Nature*, 378(6554), pp.279–81.

D'Esposito, M., Postle, B.R., Ballard, D. and Lease, J., 1999. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain and cognition*, 41(1), pp.66–86.

Daffertshofer, A., Huys, R. and Beek, P.J., 2004. Dynamical coupling between locomotion and respiration. *Biological cybernetics*, 90(3), pp.157–64.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D. and Bikson, M., 2009. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain stimulation*, 2(4), p.201–7, 207.e1.

Datta, A., Truong, D., Minhas, P., Parra, L.C. and Bikson, M., 2012. Inter-Individual

Variation during Transcranial Direct Current Stimulation and Normalization of Dose Using MRI-Derived Computational Models. *Frontiers in psychiatry*, 3(October), p.91.

Davidson, T.W., Bolic, M. and Tremblay, F., 2016. Predicting Modulation in Corticomotor Excitability and in Transcallosal Inhibition in Response to Anodal Transcranial Direct Current Stimulation. *Frontiers in human neuroscience*, 10(February), pp.1–10.

Dayan, E., Censor, N., Buch, E.R., Sandrini, M. and Cohen, L.G., 2013. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nature neuroscience*, 16(7), pp.838–44.

Desimone, R. and Duncan, J., 1995. Neural mechanisms of selective visual attention. *Annual review of neuroscience*, 18, pp.193–222.

Diamond, A., 2013. Executive Functions. *Annual review of clinical psychology*, 64, pp.135–168.

Dickstein, D.L., Kabaso, D., Rocher, A.B., Luebke, J.I., Wearne, S.L. and Hof, P.R., 2007. Changes in the structural complexity of the aged brain. *Aging cell*, 6(3), pp.275–84.

Dimitrijevic, M.R., Gerasimenko, Y. and Pinter, M.M., 1998. Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, 860, pp.360–76.

Dingwell, J.B. and Cusumano, J.P., 2010. Re-interpreting detrended fluctuation analyses of stride-to-stride variability in human walking. *Gait & posture*, 32(3), pp.348–53.

Dingwell, J.B., John, J. and Cusumano, J.P., 2010. Do humans optimally exploit redundancy to control step variability in walking? *PLoS computational biology*, 6(7), p.e1000856.

Doi, T., Asai, T., Hirata, S. and Ando, H., 2011. Dual-task costs for whole trunk movement during gait. *Gait & posture*, 33(4), pp.712–4.

Doi, T., Makizako, H., Shimada, H., Park, H., Tsutsumimoto, K., Uemura, K. and Suzuki, T., 2013. Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study. *Aging clinical and experimental research*, 25(5), pp.539–44.

Douglas, J., Noga, B., Dai, X. and Jordan, L., 1993. The effects of intrathecal administration of excitatory amino acid agonists and antagonists on the initiation of locomotion in the adult cat. *Journal of neuroscience*, 13(3), pp.990–1000.

Dreher, J.-C.J.-C. and Grafman, J., 2003. Dissociating the Roles of the Rostral Anterior Cingulate and the Lateral Prefrontal Cortices in Performing Two Tasks Simultaneously or Successively. *Cerebral Cortex*, 13(4), pp.329–339.

Drew, T., 1993. Motor Cortical Activity During Voluntary Cat . I . Cells Re lated to he Forelimbs Gait Modifications in the. *Journal of Neurophysiology*, 70(1), pp.179–199.

Dubost, V., Kressig, R.W., Gonthier, R., Herrmann, F.R., Aminian, K., Najafi, B. and Beauchet, O., 2006. Relationships between dual-task related changes in stride velocity and stride time variability in healthy older adults. *Human movement science*, 25(3), pp.372–382.

Duque, J., Labruna, L., Verset, S., Olivier, E. and Ivry, R.B., 2012. Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. *The Journal of neuroscience*, 32(3), pp.806–16.

Duysens, J. and Van de Crommert, H., 1998. Neural control of locomotion; Part 1: The central pattern generator from cats to humans. *Gait & posture*, 7(2), pp.131–141.

Eriksson, J., Vogel, E.K., Lansner, A., Bergström, F. and Nyberg, L., 2015. Neurocognitive Architecture of Working Memory. *Neuron*, 88(1), pp.33–46.

Faul, F., Erdfelder, E., Lang, A.-G. and Buchner, A., 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), pp.175–191.

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P. and Pascual-Leone, A., 2007. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *The Journal of neuroscience*, 27(46), pp.12500–5.

Fertonani, A., Brambilla, M., Cotelli, M. and Miniussi, C., 2014. The timing of cognitive plasticity in physiological aging: A tDCS study of naming. *Frontiers in aging neuroscience*, 6(JUN), pp.1–9.

Filmer, H.L., Dux, P.E. and Mattingley, J.B., 2014. Applications of transcranial direct current stimulation for understanding brain function. *Trends in Neurosciences*, 37(12), pp.742–753.

Filmer, H.L., Mattingley, J.B. and Dux, P.E., 2013. Improved multitasking following prefrontal tDCS. *Cortex*, 49(10), pp.2845–52.

Fraizer, E.V. and Mitra, S., 2008. Methodological and interpretive issues in posture-cognition dual-tasking in upright stance. *Gait & posture*, 27(2), pp.271–279.

Franz, E.A., Zelaznik, H.N., Swinnen, S.S. and Walter, C., 2001. Spatial conceptual influences on the coordination of bimanual actions: when a dual task becomes a single task. *Journal of motor behavior*, 33(1), pp.103–12.

Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T.A., Paulus, W. and Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental brain research*, 166, pp.23–30.

Frenkel-Toledo, S., Giladi, N., Peretz, C., Herman, T., Gruendlinger, L. and Hausdorff, J.M., 2005. Effect of gait speed on gait rhythmicity in Parkinson’s disease: variability of stride time and swing time respond differently. *Journal of neuroengineering and rehabilitation*, 2, p.23.

Frisk, V. and Milner, B., 1990. The relationship of working memory to the immediate recall of stories following unilateral temporal or frontal lobectomy. *Neuropsychologia*, 28(2), pp.121–135.

Frontera, W.R., Hughes, V.A., Fielding, R.A., Fiatarone, M.A., Evans, W.J. and Roubenoff, R., 2000. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol*, 88(4), pp.1321–1326.

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., Kimura, J. and Shibasaki, H., 1997. Brain functional activity during gait in normal subjects: a SPECT study. *Neuroscience letters*, 228(3), pp.183–186.

Fuster, J., 2001. The prefrontal cortex-An update-Time is of the essence. *Neuron*, 30(C), pp.319–333.

Fuster, J., 2013. Cognitve functions of the prefrontal cortex. In: D.T. Stuss and R.T. Knight, eds., *Principles of Frontal Lobe Function*. OUP USA, p.777.

Fuster, J.M., 2000. Executive frontal functions. *Experimental brain research*, 133(1), pp.66–70.

Gabell, A. and Nayak, U.S.L., 1984. The Effect of Age on Variability in Gait. *Journal of Gerontology*, 39(6), pp.662–666.

Gandiga, P.C., Hummel, F.C. and Cohen, L.G., 2006. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*, 117(4), pp.845–850.

Ganguli, M., Ratcliff, G. and Huff, F., 1990. Serial sevens versus world backwards: a comparison of the two measures of attention from the MMSE. *Journal of geriatric ...*, 3(4), pp.203–207.

George, M.S. and Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 35(1), pp.301–16.

Gibson, J., 1958. Visually controlled locomotion and visual orientation in animals. *British journal of psychology*, 49(3), pp.182–94.

Gladwin, T.E., den Uyl, T.E., Fregni, F.F. and Wiers, R.W., 2012. Enhancement of selective attention by tDCS: interaction with interference in a Sternberg task. *Neuroscience letters*, 512(1), pp.33–7.

Goble, D.J., Coxon, J.P., Wenderoth, N., Van Impe, A. and Swinnen, S.P., 2009. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. *Neuroscience and biobehavioral reviews*, 33(3), pp.271–8.

Goodpaster, B.H., Park, S.W., Harris, T.B., Kritchevsky, S.B., Nevitt, M., Schwartz, A. V., Simonsick, E.M., Tylavsky, F.A., Visser, M. and Newman, A.B., 2006. The

Loss of Skeletal Muscle Strength, Mass, and Quality in Older Adults: The Health, Aging and Body Composition Study. *The journals of gerontology Series A: biological sciences and medical sciences*, 61(10), pp.1059–1064.

Grabiner, M.D. and Troy, K.L., 2005. Attention demanding tasks during treadmill walking reduce step width variability in young adults. *Journal of neuroengineering and rehabilitation*, 2, p.25.

Grabli, D., Karachi, C., Welter, M.-L., Lau, B., Hirsch, E.C., Vidailhet, M. and François, C., 2012. Normal and pathological gait: what we learn from Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*, 83(10), pp.979–85.

Greene, B.R., Foran, T.G., Mcgrath, D., Doheny, E.P., Burns, A. and Caulfield, B., 2012. A Comparison of Algorithms for Body-Worn Sensor-Based Spatiotemporal Gait Parameters to the GAITRite Electronic Walkway. *Journal of Applied Biomechanics*, 28, pp.349–355.

Greenwood, P.M., 2000. The frontal aging hypothesis evaluated. *Journal of the International Neuropsychological Society*, 6(6), pp.705–726.

Grillner, S., 1985. Neurobiological bases of rhythmic motor acts in vertebrates. *Science (New York, N.Y.)*, 228(4696), pp.143–9.

Grillner, S. and Wallen, P., 1985. Central pattern generators with special refernce to vertebrates. *Annual review of neuroscience*, 8, pp.233–61.

Guertin, P.A., 2009. The mammalian central pattern generator for locomotion. *Brain research reviews*, 62(1), pp.45–56.

Hallett, M., 2007. Transcranial Magnetic Stimulation: A Primer. *Neuron*, 55(2), pp.187–199.

Halsband, U. and Passingham, R., 1982. The role of premotor and parietal cortex in the direction of action. *Brain research*, 240(2), pp.368–72.

Han, S.W. and Marois, R., 2013. The source of dual-task limitations: serial or parallel processing of multiple response selections? *Attention, perception & psychophysics*, 75(7), pp.1395–405.

Hasan, A., Galea, J.M., Casula, E.P., Falkai, P., Bestmann, S. and Rothwell, J.C.,

2013. Muscle and timing-specific functional connectivity between the dorsolateral prefrontal cortex and the primary motor cortex. *Journal of cognitive neuroscience*, 25(4), pp.558–570.

Hausdorff, J.M., 2001. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Archives of physical medicine and rehabilitation*, 82(8), pp.1050–6.

Hausdorff, J.M., 2005. Gait variability: methods, modeling and meaning. *Journal of neuroengineering and rehabilitation*, 2, p.19.

Hausdorff, J.M., Yogev, G., Springer, S., Simon, E.S. and Giladi, N., 2005. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Experimental brain research*, 164(4), pp.541–8.

Hazy, T.E., Frank, M.J. and O'reilly, R.C., 2007. Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 362(1485), pp.1601–13.

Hebb, D., 1949. *The organization of behavior; a neuropsychological theory*. Oxford: Wiley.

Hebb, D.O., 2005. *The Organization of Behavior: A Neuropsychological Theory*. New York, NY: John Wiley and Sons.

Herman, T., Mirelman, A., Giladi, N., Schweiger, A. and Hausdorff, J.M., 2010. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 65(10), pp.1086–92.

Herwig, U., Satrapi, P. and Sch\önfeldt-Lecuona, C., 2003. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain topography*, 16(2), pp.95–99.

Hiroshi, S., 2012. Cortical activities associated with voluntary movements and involuntary movements. *Clinical Neurophysiology*, 123(2), pp.229–243.

Hobert, M.A., Niebler, R., Meyer, S.I., Brockmann, K., Becker, C., Huber, H., Gaenslen, A., Godau, J., Eschweiler, G.W., Berg, D. and Maetzler, W., 2011. Poor trail making test performance is directly associated with altered dual task prioritization in the elderly--baseline results from the TREND study. *PLoS ONE*, 6(11), p.e27831.

Holtzer, R., Epstein, N., Mahoney, J.R., Izzetoglu, M. and Blumen, H.M., 2014. Neuroimaging of Mobility in Aging: A Targeted Review. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 69(11), pp.1375–1388.

Holtzer, R., Mahoney, J.R., Izzetoglu, M., Izzetoglu, K., Onaral, B. and Verghese, J., 2011. fNIRS study of walking and walking while talking in young and old individuals. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 66(8), pp.879–87.

de Hoon, E.W., Allum, J.H., Carpenter, M.G., Salis, C., Bloem, B.R., Conzelmann, M. and Bischoff, H.A., 2003. Quantitative assessment of the stops walking while talking test in the elderly. *Archives of Physical Medicine and Rehabilitation*, 84(6), pp.838–842.

Horvath, J.C., Carter, O. and Forte, J.D., 2014a. Transcranial direct current stimulation: five important issues we aren’t discussing (but probably should be). *Frontiers in Systems Neuroscience*, 8.

Horvath, J.C., Forte, J.D. and Carter, O., 2014b. Evidence that transcranial direct current stimulation (tDCS) Generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy Human subjects: A systematic review. *Neuropsychologia*, 66, pp.213–236.

Horvath, J.C., Forte, J.D. and Carter, O., 2015. Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain stimulation*, 8(3), pp.535–550.

Hoshi, E., 2006. Functional specialization within the dorsolateral prefrontal cortex: A review of anatomical and physiological studies of non-human primates. *Neuroscience research*, 54(2), pp.73–84.

Hoy, K.E., Emonson, M.R., Arnold, S.L., Thomson, R.H., Daskalakis, Z.J. and Fitzgerald, P.B., 2013. Testing the Limits: Investigating the effect of tDCS dose on working memory enhancement in healthy controls. *Neuropsychologia*, 51(9), pp.1777–1784.

Hsu, C.L., Nagamatsu, L.S., Davis, J.C. and Liu-Ambrose, T., 2012. Examining the relationship between specific cognitive processes and falls risk in older adults: a systematic review. *Osteoporosis international*, 23(10), pp.2409–24.

Huang, H.J. and Mercer, V.S., 2001. Dual-task methodology: applications in studies of cognitive and motor performance in adults and children. *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association*, 13(3), pp.133–40.

Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P. and Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. *Neuron*, 45(2), pp.201–6.

Huxhold, O., Li, S.-C., Schmiedek, F. and Lindenberger, U., 2006. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain research bulletin*, 69(3), pp.294–305.

Huys, R. and Beek, P.J., 2002. The coupling between point-of-gaze and ball movements in three-ball cascade juggling: the effects of expertise, pattern and tempo. *Journal of sports sciences*, 20(3), pp.171–86.

van Iersel, M.B., Ribbers, H., Munneke, M., Borm, G.F. and Rikkert, M.G.O., 2007. The Effect of Cognitive Dual Tasks on Balance During Walking in Physically Fit Elderly People. *Archives of Physical Medicine and Rehabilitation*, 88(2), pp.187–191.

IJmker, T. and Lamoth, C.J.C., 2012. Gait and cognition: The relationship between gait stability and variability with executive function in persons with and without dementia. *Gait & posture*, 35(1), pp.126–130.

Jacobson, L., Koslowsky, M. and Lavidor, M., 2012. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental brain research*, 216(1), pp.1–10.

Jaeggi, S.M., Buschkuehl, M., Perrig, W.J. and Meier, B., 2010. The concurrent validity of the N-back task as a working memory measure. *Memory (Hove, England)*, 18(4), pp.394–412.

Jagacinski, R.J., Marshburn, E., Klapp, S.T. and Jones, M.R., 1988. Tests of parallel versus integrated structure in polyrhythmic tapping. *Journal of motor behavior*, 20(4), pp.416–42.

Jahn, K., Deutschländer, A., Stephan, T., Kalla, R., Wiesmann, M., Strupp, M. and Brandt, T., 2008. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *NeuroImage*, 39(2), pp.786–92.

James, W., n.d. *The Principles Of Psychology -, Part 1*. Read Books Limited.

Jo, J.M., Kim, Y.-H., Ko, M.-H., Ohn, S.H., Joen, B. and Lee, K.H., 2009. Enhancing the Working Memory of Stroke Patients Using tDCS. *American Journal of Physical Medicine & Rehabilitation*, 88, pp.404–409.

Johnell, O. and Kanis, J., 2005. Epidemiology of osteoporotic fractures. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, 16 Suppl 2, pp.S3-7.

Johnson, J.A., Strafella, A.P. and Zatorre, R.J., 2007. The role of the dorsolateral prefrontal cortex in bimodal divided attention: two transcranial magnetic stimulation studies. *Journal of cognitive neuroscience*, 19(6), pp.907–20.

Jones, K.T., Gözenman, F. and Berryhill, M.E., 2015. The strategy and motivational influences on the beneficial effect of neurostimulation: A tDCS and fNIRS study. *NeuroImage*, 105, pp.238–247.

Jordan, K., Challis, J.H. and Newell, K.M.K.M., 2007. Walking speed influences on gait cycle variability. *Gait & posture*, 26(1), pp.128–134.

Jurado, M.B. and Rosselli, M., 2007. The elusive nature of executive functions: a review of our current understanding. *Neuropsychology review*, 17(3), pp.213–33.

Kadosh, R.C., 2013. Using transcranial electrical stimulation to enhance cognitive functions in the typical and atypical brain. *Translational Neuroscience*, 4(1), pp.20–33.

Kahneman, D., 1973. Attention and Effort.

Kang, H.G. and Dingwell, J.B., 2008. Effects of walking speed, strength and range of motion on gait stability in healthy older adults. *Journal of Biomechanics*, 41(14), pp.2899–2905.

Kavanagh, J.J., 2009. Lower trunk motion and speed-dependence during walking. *Journal of neuroengineering and rehabilitation*, 6(1), p.9.

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., Brunelin, J., Möller, H.-J.H.J., Reiser, M. and Padberg, F., 2011a. Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. *The Journal of neuroscience*, 31(43), pp.15284–15293.

Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., Karch, S., Möller, H.J., Nitsche, M. a. and Mulert, C., 2011b. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study. *NeuroImage*, 55(2), pp.644–657.

Kellaway, P., 1946. The part played by electric fish in the early history of bioelectricity and electrotherapy. *Bulletin of the history of medicine*, 20(2), pp.112–37.

Kelly, V.E., Eusterbrock, A.J. and Shumway-Cook, A., 2013. Factors influencing dynamic prioritization during dual-task walking in healthy young adults. *Gait & posture*, 37(1), pp.131–134.

Kelly, V.E., Janke, A.A. and Shumway-Cook, A., 2010. Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Experimental brain research*, 207(1–2), pp.65–73.

Klapp, S.T., Nelson, J.M. and Jagacinski, R.J., 1998. Can people tap concurrent bimanual rhythms independently? *Journal of motor behavior*, 30(4), pp.301–22.

Koenraadt, K.L.M., Roelofsen, E.G.J., Duysens, J. and Keijsers, N.L.W., 2014. Cortical control of normal gait and precision stepping: An fNIRS study. *NeuroImage*, 85(1), pp.415–422.

Krause, B., Cohen Kadosh, R. and Kadosh, R.C., 2014. Not all brains are created equal : The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*, 8.

Krause, B., Márquez-Ruiz, J. and Kadosh, R.C., 2013. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? *Frontiers in human neuroscience*, 7, p.602.

Kuo, M.-F. and Nitsche, M.A., 2012. Effects of transcranial electrical stimulation on cognition. *Clinical EEG and neuroscience*, 43(3), pp.192–9.

de Laat, K.F., Tuladhar, A.M., van Norden, A.G.W., Norris, D.G., Zwiers, M.P. and de Leeuw, F.-E., 2011. Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. *Brain*, 134(Pt 1), pp.73–83.

Laessoe, U., Hoeck, H.C., Simonsen, O. and Voigt, M., 2008. Residual attentional capacity amongst young and elderly during dual and triple task walking. *Human movement science*, 27(3), pp.496–512.

Lajoie, Y., Teasdale, N., Bard, C. and Fleury, M., 1993. Attentional demands for static and dynamic equilibrium. *Experimental brain research*, 97(1), pp.139–144.

Lakens, D., 2013. Sailing From the Seas of Chaos Into the Corridor of Stability: Practical Recommendations to Increase the Informational Value of Studies. *Frontiers in Psychology*, 4(November), pp.1–12.

Lakens, D. and Evers, E.R.K., 2014. Sailing From the Seas of Chaos Into the Corridor of Stability: Practical Recommendations to Increase the Informational Value of Studies. *Perspectives on psychological science*, 9(3), pp.278–92.

Lang, N., Nitsche, M.A., Dileone, M., Mazzone, P., De Andrés-Arés, J., Diaz-Jara, L., Paulus, W., Di Lazzaro, V. and Oliviero, A., 2011. Transcranial direct current stimulation effects on I-wave activity in humans. *Journal of neurophysiology*, 105(6), pp.2802–10.

Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N. and Frackowiak, R.S., 2005. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *The European journal of neuroscience*, 22(2), pp.495–504.

Di Lazzaro, V., 2004. The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clinical Neurophysiology*, 115(2), pp.255–266.

Di Lazzaro, V., Profice, P., Ranieri, F., Capone, F., Dileone, M., Oliviero, A. and Pilato, F., 2012. I-wave origin and modulation. *Brain stimulation*, 5(4), pp.512–525.

Di Lazzaro, V. and Rothwell, J.C., 2014. Cortico-spinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. *The Journal of physiology*, 19, pp.4115–4128.

Learmonth, G., Thut, G., Benwell, C.S.Y. and Harvey, M., 2015. The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. *Neuropsychologia*, 74, pp.108–119.

Lee, S.J. and Hidler, J., 2008. Biomechanics of overground vs. treadmill walking in healthy individuals. *Journal of applied physiology*, 104(3), pp.747–55.

Leitner, Y., Barak, R., Giladi, N., Peretz, C., Eshel, R., Gruendlinger, L. and Hausdorff, J.M., 2007. Gait in attention deficit hyperactivity disorder : effects of methylphenidate and dual tasking. *Journal of neurology*, 254(10), pp.1330–8.

Lemon, R.N., 2008. Descending pathways in motor control. *Annual review of neuroscience*, 31, pp.195–218.

Levine, D., Richards, J. and Whittle, M.W., 2012. *Whittle's Gait Analysis*. Elsevier Health Sciences.

Lezak, M.D., 2004. *Neuropsychological Assessment*. Oxford University Press.

Li, L.M., Uehara, K. and Hanakawa, T., 2015. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in cellular Neuroscience*, 9, p.181.

Li, W., Keegan, T.H.M., Sternfeld, B., Sidney, S., Quesenberry, C.P. and Kelsey, J.L., 2006. Outdoor falls among middle-aged and older adults: a neglected public health problem. *American journal of public health*, 96(7), pp.1192–200.

Liebetanz, D., Nitsche, M.A., Tergau, F. and Paulus, W., 2002. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, 125(Pt 10), pp.2238–47.

Liston, M.B., Bergmann, J.H., Keating, N., Green, D.A. and Pavlou, M., 2014.

Postural prioritization is differentially altered in healthy older compared to younger adults during visual and auditory coded spatial multitasking. *Gait & posture*, 39(1), pp.198–204.

Liu-Ambrose, T.Y., Ashe, M.C., Graf, P., Beattie, B.L. and Khan, K.M., 2008. Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Physical therapy*, 88(12), pp.1482–91.

Logan, G.D. and Gordon, R.D., 2001. *Executive Control of Attention in Dual-Task Situations*. *Psychological Review*, .

Logie, R.H., Cocchini, G., Delia Sala, S. and Baddeley, A.D., 2004. Is there a specific executive capacity for dual task coordination? Evidence from Alzheimer's disease. *Neuropsychology*, 18(3), pp.504–13.

López-Alonso, V., Cheeran, B., Río-Rodríguez, D. and Fernández-Del-Olmo, M., 2014. Inter-individual Variability in Response to Non-invasive Brain Stimulation Paradigms. *Brain stimulation*, 7(3), pp.372–80.

López-Alonso, V., Fernández-Del-Olmo, M., Costantini, A., Gonzalez-Henriquez, J.J. and Cheeran, B., 2015. Intra-individual variability in the response to anodal transcranial direct current stimulation. *Clinical Neurophysiology*, 126, pp.2342–2347.

Lövdén, M., Schaefer, S., Pohlmeyer, A.E. and Lindenberger, U., 2008. Walking Variability and Working-Memory Load in Aging: A Dual-Process Account Relating Cognitive Control to Motor Control Performance. *The journals of gerontology Series B: psychological sciences and social sciences*, 63(3), pp.121–128.

Lu, C.-F., Liu, Y.-C., Yang, Y.-R., Wu, Y.-T. and Wang, R.-Y., 2015. Maintaining Gait Performance by Cortical Activation during Dual-Task Interference: A Functional Near-Infrared Spectroscopy Study. *PLoS ONE*, 10(6), p.e0129390.

Luber, B., 2014. Neuroenhancement by noninvasive brain stimulation is not a net zero-sum proposition. *Frontiers in Systems Neuroscience*, 8.

Lundin-Olsson, L., Nyberg, L. and Gustafson, Y., 1997. 'Stops walking when talking' as a predictor of falls in elderly people. *Lancet*, 349(9052), p.617.

MacPherson, S., Phillips, L. and Della Sala, S., 2002. Age, executive function, and social decision making: a dorsolateral prefrontal theory of cognitive aging. *Psychology and aging*, 17(4), pp.598–609.

Malcolm, B.R., Foxe, J.J., Butler, J.S. and De Sanctis, P., 2015. The aging brain shows less flexible reallocation of cognitive resources during dual-task walking: A mobile brain/body imaging (MoBI) study. *NeuroImage*, 117, pp.230–242.

Malouin, F., Richards, C.L., Jackson, P.L., Dumas, F. and Doyon, J., 2003. Brain activations during motor imagery of locomotor-related tasks: a PET study. *Human brain mapping*, 19(1), pp.47–62.

Mancini, M., Salarian, A., Carlson-Kuhta, P., Zampieri, C., King, L., Chiari, L. and Horak, F.B., 2012. ISway: a sensitive, valid and reliable measure of postural control. *Journal of neuroengineering and rehabilitation*, 9, p.59.

Mandrick, K., Derosiere, G., Dray, G., Coulon, D., Micallef, J.-P. and Perrey, S., 2013. Prefrontal cortex activity during motor tasks with additional mental load requiring attentional demand: a near-infrared spectroscopy study. *Neuroscience research*, 76(3), pp.156–162.

Manor, B., Zhou, J., Jor'dan, A., Zhang, J., Fang, J. and Pascual-Leone, A., 2016. Reduction of Dual-task Costs by Noninvasive Modulation of Prefrontal Activity in Healthy Elders. *Journal of cognitive neuroscience*, 28(2), pp.275–81.

Marshall, L., Mölle, M., Siebner, H.R. and Born, J., 2005. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. *BMC neuroscience*, 6(1), p.23.

McCambridge, A.B., Stinear, J.W. and Byblow, W.D., 2015. 'I-wave' recruitment determines response to tDCS in the upper limb, but only so far. *Brain stimulation*, 8(6), pp.1124–1129.

Meester, D., Al-yahya, E., Dawes, H., Martin-fagg, P. and Piñon, C., 2014. Associations between prefrontal cortex activation and H-reflex modulation. *Frontiers in human neuroscience*, 8(78).

Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., Flaisch, T. and Flöel, A., 2012. Electrical Brain Stimulation Improves Cognitive Performance by Modulating Functional Connectivity and Task-Specific Activation.

The Journal of neuroscience, 32(5), pp.1859–1866.

Merchant, H., Battaglia-Mayer, A. and Georgopoulos, A.P., 2003. Functional Organization of Parietal Neuronal Responses to Optic-Flow Stimuli. *Journal of neurophysiology*, 90(2), pp.675–682.

Milham, M.P., Banich, M.T. and Barad, V., 2003. Competition for priority in processing increases prefrontal cortex ' s involvement in top-down control : an event-related fMRI study of the stroop task. *Cognitive Brain Research*, 17(2), pp.212–222.

Miller, E.K., 2000. The prefrontal cortex and cognitive control. *Neuroscience*, 1(October), pp.13–15.

Miller, E.K. and Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, 24, pp.167–202.

Miller, J., Ulrich, R. and Rolke, B., 2009. On the optimality of serial and parallel processing in the psychological refractory period paradigm: Effects of the distribution of stimulus onset asynchronies. *Cognitive Psychology*, 58(3), pp.273–310.

Miniussi, C., Harris, J.A. and Ruzzoli, M., 2013. Modelling Non-Invasive Brain Stimulation in Cognitive Neuroscience. *Neuroscience and biobehavioral reviews*, 37(8), pp.1702–1712.

Miranda, P.C., Lomarev, M. and Hallett, M., 2006. Modeling the current distribution during transcranial direct current stimulation. *Clinical Neurophysiology*, 117(7), pp.1623–1629.

Mirelman, A., Maidan, I., Bernad-Elazari, H., Nieuwhof, F., Reelick, M., Giladi, N. and Hausdorff, J.M., 2014. Increased frontal brain activation during walking while dual tasking: an fNIRS study in healthy young adults. *Journal of neuroengineering and rehabilitation*, 11(1), p.85.

Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A. and Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex 'Frontal Lobe' tasks: a latent variable analysis. *Cognitive psychology*, 41(1), pp.49–100.

Monakow, K.H., Akert, K. and Künzle, H., 1979. Projections of precentral and premotor cortex to the red nucleus and other midbrain areas in Macaca fascicularis. *Experimental brain research*, 34(1), pp.91–105.

Monno, A., Temprado, J.-J., Zanone, P.-G. and Laurent, M., 2002. The interplay of attention and bimanual coordination dynamics. *Acta psychologica*, 110(2–3), pp.187–211.

Montero-Odasso, M. and Hachinski, V., 2014. Preludes to brain failure: executive dysfunction and gait disturbances. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 35(4), pp.601–4.

Montero-Odasso, M., Oteng-Amoako, A., Speechley, M., Gopaul, K., Beauchet, O., Annweiler, C. and Muir-Hunter, S.W., 2014. The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study. *The journals of gerontology Series A: biological sciences and medical sciences*, 69(13), pp.1415–1421.

Montero-Odasso, M., Verghese, J., Beauchet, O. and Hausdorff, J.M., 2012. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *Journal of the american geriatrics society*, 60(11), pp.2127–36.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., Vergari, M., Zago, S. and Priori, A., 2008. Improved naming after transcranial direct current stimulation in aphasia. *Journal of neurology, neurosurgery, and psychiatry*, 79(4), pp.451–3.

Morton, S.M. and Bastian, A.J., 2004. Cerebellar control of balance and locomotion. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, 10(3), pp.247–59.

Morton, S.M. and Bastian, A.J., 2007. Mechanisms of cerebellar gait ataxia. *Cerebellum*, 6(1), pp.79–86.

Muir-Hunter, S.W. and Wittwer, J.E., 2016. Dual-task testing to predict falls in community-dwelling older adults: a systematic review. *Physiotherapy*, 102(1), pp.29–40.

Muir, S.W., Gopaul, K. and Montero Odasso, M.M., 2012. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age and ageing*, 41(3), pp.299–308.

Nachev, P., Kennard, C. and Husain, M., 2008. Functional role of the supplementary and pre-supplementary motor areas. *Nature reviews neuroscience*, 9(11), pp.856–69.

Navon, D. and Miller, J., 1987. Role of outcome conflict in dual-task interference. *Journal of experimental psychology. Human perception and performance*, 13(3), pp.435–48.

Navon, D. and Miller, J., 2002. Queuing or sharing? A critical evaluation of the single-bottleneck notion. *Cognitive psychology*, 44(3), pp.193–251.

Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C. and Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, affective & behavioral neuroscience*, 12(2), pp.241–68.

Nieratschker, V., Kiefer, C., Giel, K., Krüger, R. and Plewnia, C., 2015. The COMT Val/Met Polymorphism Modulates Effects of tDCS on Response Inhibition. *Brain stimulation*, 8(2), pp.283–288.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F. and others, 2008. Transcranial direct current stimulation: state of the art 2008. *Brain stimulation*, 1(3), pp.206–23.

Nitsche, M.A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F. and Paulus, W., 2004. Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 29(8), pp.1573–8.

Nitsche, M.A. and Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, 57(10), p.1899.

Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W. and Tergau, F., 2003a. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of cognitive neuroscience*, 15(4), pp.619–626.

Nitsche, M. a, Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F. and Paulus, W., 2003b. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of physiology*, 553(Pt 1), pp.293–301.

Nitsche, M. a, Müller-Dahlhaus, F., Paulus, W. and Ziemann, U., 2012. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. *The Journal of physiology*, 590(Pt 19), pp.4641–62.

Nitsche, M. and Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology*, 527(3), p.633.

Nitsche, M.S.M. a, Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W. and Tergau, F., 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of physiology*, 568(Pt 1), pp.291–303.

Norman, D. and Shalice, T., 1986. Attention to Action: Willed and Automatic Control of Behavior. In: R.J. Davidson, G.E. Schwartz and D. Shapiro, eds., *Consciousness and Self-Regulation*. Boston, MA: Springer US, pp.1–18.

Nutt, J.G., 2013. Higher-level gait disorders: An open frontier. *Movement disorders*, 28(11), pp.1560–5.

Nutt, J.G., Marsden, C.D. and Thompson, P.D., 1993. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology*, 43(2), pp.268–79.

Office for National Statistics, 2012. Population Ageing in the United Kingdom , its Constituent Countries and the European Union. (March), pp.1–12.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), pp.97–113.

Opitz, A., Paulus, W., Will, S., Antunes, A. and Thielscher, A., 2015. Determinants of the electric field during transcranial direct current stimulation. *NeuroImage*, 109, pp.140–50.

Owen, A.M., McMillan, K.M., Laird, A.R. and Bullmore, E., 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, 25(1), pp.46–59.

Pahapill, P.A., 2000. The pedunculopontine nucleus and Parkinson's disease. *Brain*, 123(9), pp.1767–1783.

Pascual-Leone, A., Walsh, V. and Rothwell, J., 2000. Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Current Opinion in neurobiology*, 10(2), pp.232–7.

Pashler, H., 1984. Processing stages in overlapping tasks: Evidence for a central bottleneck. *Journal of Experimental Psychology: Human Perception and Performance*, 10(3), pp.358–377.

Pashler, H., 1990. Do response modality effects support multiprocessor models of divided attention? *Journal of experimental psychology. Human perception and performance*, 16(4), pp.826–42.

Pashler, H., 1994. Dual-task interference in simple tasks: data and theory. *Psychological bulletin*, 116(2), pp.220–44.

Pashler, H. and Johnston, J.C., 1989. Chronometric evidence for central postponement in temporally overlapping tasks. *The Quarterly Journal of Experimental Psychology Section A*, 41(1), pp.19–45.

Passingham, R.E., Rowe, J.B. and Sakai, K., 2013. Has brain imaging discovered anything new about how the brain works? *NeuroImage*, 66, pp.142–50.

Passingham, R.E. and Wise, S.P., 2012. *The Neurobiology of the Prefrontal Cortex: Anatomy, Evolution, and the Origin of Insight*. OUP Oxford.

Pearson, K.G., Misiaszek, J.E. and Fouad, K., 1998. Enhancement and resetting of locomotor activity by muscle afferents. *Annals of the New York Academy of Sciences*, 860, pp.203–15.

Peña-Gómez, C., Sala-Lonch, R., Junqué, C., Clemente, I.C., Vidal, D., Bargalló, N., Falcón, C., Valls-Solé, J., Pascual-Leone, Á., Bartrés-Faz, D. and Pascual-Leone, A., 2012. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain stimulation*, 5(3), pp.252–263.

Perry, R.J., Watson, P. and Hodges, J.R., 2000. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia*, 38(3), pp.252–71.

Petersen, N.T., Butler, J.E., Marchand-Pauvert, V., Fisher, R., Ledebt, A., Pyndt, H.S., Hansen, N.L. and Nielsen, J.B., 2001. Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *The Journal of physiology*, 537(Pt 2), pp.651–6.

Pichierri, G., Wolf, P., Murer, K. and de Bruin, E.D., 2011. Cognitive and cognitive-motor interventions affecting physical functioning: a systematic review. *BMC geriatrics*, 11(1), p.29.

Plummer-D'Amato, P., Altmann, L.J.P., Saracino, D., Fox, E., Behrman, A.L. and Marsiske, M., 2008. Interactions between cognitive tasks and gait after stroke: a dual task study. *Gait & posture*, 27(4), pp.683–8.

Polanía, R., Nitsche, M.A. and Paulus, W., 2011a. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Human brain mapping*, 32(8), pp.1236–49.

Polanía, R., Paulus, W., Antal, A. and Nitsche, M.A., 2011b. Introducing graph theory to track for neuroplastic alterations in the resting human brain: A transcranial direct current stimulation study. *NeuroImage*, 54(3), pp.2287–2296.

Polanía, R., Paulus, W. and Nitsche, M. a, 2012. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Human brain mapping*, 33(10), pp.2499–508.

Poldrack, R. a. and Farah, M.J., 2015. Progress and challenges in probing the human brain. *Nature*, 526(7573), pp.371–379.

Poreisz, C., Boros, K., Antal, A. and Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain research bulletin*, 72(4–6), pp.208–214.

Prince, F., Corriveau, H., Hébert, R. and Winter, D.A., 1997. Gait in the elderly. *Gait & posture*, 5(2), pp.128–135.

Raymond, J.E., Shapiro, K.L. and Arnell, K.M., 1992. Temporary suppression of visual processing in an RSVP task: an attentional blink? . *Journal of experimental psychology. Human perception and performance*, 18(3), pp.849–60.

Repovs, G. and Baddeley, A., 2006. The multi-component model of working memory: explorations in experimental cognitive psychology. *Neuroscience*, 139(1), pp.5–21.

Riley, P.O., Paolini, G., Della Croce, U., Paylo, K.W. and Kerrigan, D.C., 2007. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait & posture*, 26(1), pp.17–24.

Rorden, C. and Karnath, H.-O., 2004. Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nature reviews neuroscience*, 5(10), pp.813–9.

Rosa, R.R., Colligan, M.J. and Lewis, P., 1989. Extended workdays: Effects of 8-hour and 12-hour rotating shift schedules on performance, subjective alertness, sleep patterns, and psychosocial variables. *Work & Stress*, 3(1), pp.21–32.

Rosano, C., Studenski, S. a, Aizenstein, H.J., Boudreau, R.M., Longstreth, W.T. and Newman, A.B., 2012. Slower gait, slower information processing and smaller prefrontal area in older adults. *Age and ageing*, 41(1), pp.58–64.

Rossi, S., Hallett, M., Rossini, P.M. and Pascual-Leone, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 120(12), pp.2008–2039.

Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijević, M.R., Hallett, M., Katayama, Y. and Lücking, C.H., 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and clinical neurophysiology*, 91(2), pp.79–92.

Russoa, R., Wallace, D., Fitzgerald, P.B., Cooper, N.R., Russo, R., Wallace, D., Fitzgerald, P.B., Cooper, N.R., Russoa, R., Wallace, D., Fitzgerald, P.B., Cooper, N.R. and Russo, R., 2013. Perception of Comfort During Active and Sham

Transcranial Direct Current Stimulation: A Double Blind Study. *Brain stimulation*, 6(June), pp.1–6.

Ruthruff, E., Johnston, J.C., Van Selst, M., Whitsell, S. and Remington, R., 2003. Vanishing dual-task interference after practice: has the bottleneck been eliminated or is it merely latent? *Journal of experimental psychology. Human perception and performance*, 29(2), pp.280–289.

Salarian, A., Horak, F.B., Zampieri, C., Carlson-Kuhta, P., Nutt, J.G. and Aminian, K., 2010. iTUG, a sensitive and reliable measure of mobility. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 18(3), pp.303–10.

Salarian, A., Russmann, H., Vingerhoets, F.J.G., Dehollain, C., Blanc, Y., Burkhard, P.R. and Aminian, K., 2004. Gait assessment in Parkinson’s disease: toward an ambulatory system for long-term monitoring. *IEEE transactions on bio-medical engineering*, 51(8), pp.1434–43.

Salthouse, T.A., 2011. Neuroanatomical substrates of age-related cognitive decline. *Psychological bulletin*, 137(5), pp.753–84.

Schaefer, S., Lövdén, M., Wieckhorst, B. and Lindenberger, U., 2010. Cognitive performance is improved while walking: Differences in cognitive–sensorimotor couplings between children and young adults. *European Journal of Developmental Psychology*, 7(3), pp.371–389.

Schluter, N.D., Rushworth, M.F., Passingham, R.E. and Mills, K.R., 1998. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain*, 121 (Pt 5, pp.785–99.

Schoene, D., Valenzuela, T., Lord, S.R. and de Bruin, E.D., 2014. The effect of interactive cognitive-motor training in reducing fall risk in older people: a systematic review. *BMC Geriatrics*, 14(1), p.107.

Schulz, R., Gerloff, C. and Hummel, F.C., 2012. Non-invasive brain stimulation in neurological diseases. *Neuropharmacology*, 64, pp.579–587.

Schwenk, M., Zieschang, T., Oster, P. and Hauer, K., 2010. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology*, 74(24), pp.1961–8.

Scuffham, P., 2003. Incidence and costs of unintentional falls in older people in the United Kingdom. *Journal of Epidemiology & Community Health*, 57(9), pp.740–744.

Van Selst, M., Ruthruff, E. and Johnston, J.C., 1999. Can practice eliminate the psychological refractory period effect? *Journal of experimental psychology. Human perception and performance*, 25(5), pp.1268–83.

Shapiro, K.L., Raymond, J.E. and Arnell, K.M., 1997. The attentional blink. *Trends in cognitive sciences*, 1(8), pp.291–6.

Sheik-Nainar, M.A. and Kaber, D.B., 2007. The Utility of a Virtual Reality Locomotion Interface for Studying Gait Behavior. *Human Factors*, 49(4), pp.696–709.

Sheridan, P.L., Solomont, J., Kowall, N. and Hausdorff, J.M., 2003. Influence of Executive Function on Locomotor Function: Divided Attention Increases Gait Variability in Alzheimer's Disease. *Journal of the american geriatrics society*, 51(11), pp.1633–1637.

Shiffrin, R.M. and Schneider, W., 1976. Controlled and Automatic Human Information Processing: 11. Perceptual Learning, Automatic Attending, and a General Theory. *Psychological Review*, 84(2), pp.127–190.

Shik, M.L. and Orlovsky, G.N., 1976. Neurophysiology of locomotor automatism. *Physiological reviews*, 56(3), pp.465–501.

Shumway-Cook, A., Woollacott, M., Kerns, K.A. and Baldwin, M., 1997. The Effects of Two Types of Cognitive Tasks on Postural Stability in Older Adults With and Without a History of Falls. *The journals of gerontology Series A: biological sciences and medical sciences*, 52A(4), pp.M232–M240.

Silsupadol, P., Shumway-Cook, A., Lugade, V., van Donkelaar, P., Chou, L.-S., Mayr, U. and Woollacott, M.H., 2009. Effects of single-task versus dual-task training on balance performance in older adults: a double-blind, randomized controlled trial. *Archives of physical medicine and rehabilitation*, 90(3), pp.381–7.

Simoni, D., Rubbieri, G., Baccini, M., Rinaldi, L., Becheri, D., Forconi, T., Mossello, E., Zanieri, S., Marchionni, N. and Di Bari, M., 2013. Different motor tasks impact differently on cognitive performance of older persons during dual task tests. *Clinical biomechanics*, 28(6), pp.692–6.

Smith, M.C., 1967. Stimulus-response compatibility and parallel response selection. *Canadian journal of psychology*, 21(6), pp.496–503.

Sparrow, W.A., Bradshaw, E.J., Lamoureux, E. and Tirosh, O., 2002. Ageing effects on the attention demands of walking. *Human movement science*, 21(5–6), pp.961–972.

Springer, S., Giladi, N., Peretz, C., Yogev, G., Simon, E.S. and Hausdorff, J.M., 2006. Dual tasking effects on gait variability: The role of aging, falls, and executive function. *Movement disorders*, 21(7), pp.950–957.

Stagg, C., Best, J. and Stephenson, M., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The journal of neuroscience*, 29(16), pp.5202–5206.

Stagg, C.J., Lin, R.L., Mezue, M., Segerdahl, A., Kong, Y., Xie, J. and Tracey, I., 2013. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. *The Journal of neuroscience*, 33(28), pp.11425–31.

Stagg, C.J. and Nitsche, M.A., 2011. Physiological basis of transcranial direct current stimulation. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, 17(1), pp.37–53.

Stocks, N., 2000. Suprathreshold stochastic resonance in multilevel threshold systems. *Physical review letters*, 84(11), pp.2310–3.

Strayer, D.L. and Johnston, W.A., 2001. Driven to Distraction: Dual-Task Studies of Simulated Driving and Conversing on a Cellular Telephone. *Psychological Science*, 12(6), pp.462–466.

Strobach, T., Soutschek, A., Antonenko, D., Flöel, A. and Schubert, T., 2015. Modulation of executive control in dual tasks with transcranial direct current stimulation (tDCS). *Neuropsychologia*, 68(Febuary), pp.8–20.

Suzuki, M., Miyai, I., Ono, T. and Kubota, K., 2008. Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *NeuroImage*, 39(2), pp.600–7.

Suzuki, M., Miyai, I., Ono, T., Oda, I., Konishi, I., Kochiyama, T. and Kubota, K., 2004. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. *NeuroImage*, 23(3), pp.1020–1026.

Szameitat, A.A.J., Schubert, T., Müller, K. and Von Cramon, D.Y., 2002. Localization of executive functions in dual-task performance with fMRI. *Journal of cognitive neuroscience*, 14(8), pp.1184–1199.

Szturm, T., Maharjan, P., Marotta, J.J., Shay, B., Shrestha, S. and Sakhalkar, V., 2013. The interacting effect of cognitive and motor task demands on performance of gait, balance and cognition in young adults. *Gait & posture*, 38(4), pp.596–602.

Tabachnick, B.G. and Fidell, L.S., 2007. *Using multivariate statistics (5th ed.).* Boston MA: Allyn & Bacon/Pearson Education.

Takakusaki, K., 2013. Neurophysiology of gait: From the spinal cord to the frontal lobe. *Movement disorders*, 28(11), pp.1483–91.

Takakusaki, K., Saitoh, K., Harada, H. and Kashiwayanagi, M., 2004. Role of basal ganglia-brainstem pathways in the control of motor behaviors. *Neuroscience research*, 50(2), pp.137–51.

Takano, N., 1995. Phase relation and breathing pattern during locomotor/respiratory coupling in uphill and downhill running. *Japanese Journal of Physiology*, 45(1), pp.47–58.

Takeuchi, N., Mori, T., Suzukamo, Y., Tanaka, N. and Izumi, S.-I., 2016. Parallel processing of cognitive and physical demands in left and right prefrontal cortices during smartphone use while walking. *BMC Neuroscience*, 17(1), p.9.

Tanji, J. and Hoshi, E., 2008. Role of the Lateral Prefrontal Cortex in Executive Behavioral Control. *Physiological reviews*, 88(140), pp.37–57.

Telford, C.W., 1931. The refractory phase of voluntary and associative responses. *Journal of Experimental Psychology*, 14(1), pp.1–36.

Teo, F., Hoy, K.E., Daskalakis, Z.J. and Fitzgerald, P.B., 2011. Investigating the Role of Current Strength in tDCS Modulation of Working Memory Performance in Healthy Controls. *Frontiers in Psychiatry*, 2, p.45.

Tombu, M. and Jolicœur, P., 2003. A Central Capacity Sharing Model of Dual-Task Performance. *Journal of Experimental Psychology. Human Perception & Performance. Feb2003*, 29(1), pp.3–19.

Tremblay, S., Lepage, J.-F., Latulipe-Loiselle, A., Fregni, F., Pascual-Leone, A. and Théoret, H., 2014. The uncertain outcome of prefrontal tDCS. *Brain stimulation*, 7(6), pp.773–83.

Truong, D.Q., Magerowski, G., Blackburn, G.L., Bikson, M. and Alonso-Alonso, M., 2013. Computational modeling of transcranial direct current stimulation (tDCS) in obesity: Impact of head fat and dose guidelines. *NeuroImage. Clinical*, 2, pp.759–66.

Tseng, P., Hsu, T.-Y., Chang, C.-F., Tzeng, O.J.L., Hung, D.L., Muggleton, N.G., Walsh, V., Liang, W.-K., Cheng, S. and Juan, C.-H., 2012. Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *The Journal of neuroscience*, 32(31), pp.10554–61.

Tunovic, S., Press, D.Z. and Robertson, E.M., 2014. A physiological signal that prevents motor skill improvements during consolidation. *The Journal of neuroscience*, 34(15), pp.5302–10.

Vaseghi, B., Zoghi, M. and Jaberzadeh, S., 2015a. Differential effects of cathodal transcranial direct current stimulation of prefrontal, motor and somatosensory cortices on cortical excitability and pain perception - a double-blind randomised sham-controlled study. *European Journal of Neuroscience*, 42(7), pp.2426–2437.

Vaseghi, B., Zoghi, M. and Jaberzadeh, S., 2015b. The effects of anodal-tDCS on corticospinal excitability enhancement and its after-effects: conventional vs. unihemispheric concurrent dual-site stimulation. *Frontiers in human neuroscience*, 9(September), pp.1–13.

Verbruggen, F., McLaren, I.P.L. and Chambers, C.D., 2014. Banishing the Control

Homunculi in Studies of Action Control and Behavior Change. *Perspectives on Psychological Science*, 9(5), pp.497–524.

Verghese, J., Mahoney, J., Ambrose, A.F., Wang, C. and Holtzer, R., 2010. Effect of cognitive remediation on gait in sedentary seniors. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 65(12), pp.1338–43.

Verrel, J., Lövdén, M., Schellenbach, M., Schaefer, S. and Lindenberger, U., 2009. Interacting effects of cognitive load and adult age on the regularity of whole-body motion during treadmill walking. *Psychology and aging*, 24(1), pp.75–81.

Villard, S., Casties, J.F. and Mottet, D., 2005. Dynamic stability of locomotor respiratory coupling during cycling in humans. *Neuroscience letters*, 383(3), pp.333–338.

Vines, B., Schnider, N. and Schlaug, G., 2006. Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. *Neuroreport*, 17(10), pp.1047–1050.

Volz, L.J., Hamada, M., Rothwell, J.C. and Grefkes, C., 2015. What Makes the Muscle Twitch: Motor System Connectivity and TMS-Induced Activity. *Cerebral Cortex*, 25(9), pp.2346–2353.

Wager, T.D. and Smith, E.E., 2003. Neuroimaging studies of working memory. *Cognitive, Affective, & Behavioral Neuroscience*, 3(4), pp.255–274.

Walsh, V. and Cowey, A., 2000. Transcranial magnetic stimulation and cognitive neuroscience. *Nature reviews neuroscience*, 1(1), pp.73–9.

Warren, W.H., Kay, B.A., Zosh, W.D., Duchon, A.P. and Sahuc, S., 2001. Optic flow is used to control human walking. *Nature neuroscience*, 4(2), pp.213–6.

Weiss, M. and Lavidor, M., 2012. When Less Is More: Evidence for a Facilitative Cathodal tDCS Effect in Attentional Abilities. *Journal of cognitive neuroscience*, 24(9), pp.1826–33.

Welford, A.T., 1952. The ‘psychological refractory period’ and the timing of high-speed performance—a review and a theory. *British Journal of Psychology.*, 43(1), pp.2–19.

West, R.L., 1996. An application of prefrontal cortex function theory to cognitive aging. *Psychological bulletin*, 120(2), pp.272–292.

Wickens, C.D., 2002. Multiple resources and performance prediction. *Theoretical Issues in Ergonomics Science*, 3(2), pp.159–177.

Wiethoff, S., Hamada, M. and Rothwell, J.C., 2014. Variability in Response to Transcranial Direct Current Stimulation of the Motor Cortex. *Brain stimulation*, 7(3), pp.468–475.

Wilson, R.S., Beckett, L.A., Barnes, L.L., Schneider, J.A., Bach, J., Evans, D.A. and Bennett, D.A., 2002. Individual differences in rates of change in cognitive abilities of older persons. *Psychology and aging*, 17(2), pp.179–93.

Winter, D., 1991. *Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological*. Waterloo Biomechanics.

Winter, D., 1995. Human balance and posture control during standing and walking. *Gait & posture*, 3(4), pp.193–214.

Wirth, M., Rahman, R.A., Kuenecke, J., Koenig, T., Horn, H., Sommer, W. and Dierks, T., 2011. Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. *Neuropsychologia*, 49(14), pp.3989–3998.

Woollacott, M. and Shumway-Cook, A., 2002. Attention and the control of posture and gait: a review of an emerging area of research. *Gait & posture*, 16(1), pp.1–14.

Wrightson, J.G., Ross, E.Z. and Smeeton, N.J., 2016. The Effect of Cognitive Task Type and Walking Speed on Dual-Task Gait in Healthy Adults. *Motor control*, 20(1), pp.109–21.

Wrightson, J.G., Twomey, R., Ross, E.Z. and Smeeton, N.J., 2015. The effect of transcranial direct current stimulation on task processing and prioritisation during dual-task gait. *Experimental brain research*, 233(5), pp.1575–1583.

Yamada, M., Aoyama, T., Arai, H., Nagai, K., Tanaka, B., Uemura, K., Mori, S. and Ichihashi, N., 2011. Dual-task walk is a reliable predictor of falls in robust elderely adults. *Journal of the american geriatrics society*, 59(1), pp.163–164.

Yang, J.F. and Gorassini, M., 2006. Spinal and brain control of human walking: implications for retraining of walking. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, 12(5), pp.379–89.

Yildiz, A. and Beste, C., 2015. Parallel and serial processing in dual-tasking differentially involves mechanisms in the striatum and the lateral prefrontal cortex. *Brain Structure and Function*, 220(6), pp.3131–3142.

Yogev-Seligmann, G., Hausdorff, J.M. and Giladi, N., 2008. The role of executive function and attention in gait. *Movement disorders*, 23(3), pp.329–42.

Yogev-Seligmann, G., Rotem-Galili, Y., Mirelman, A., Dickstein, R., Giladi, N. and Hausdorff, J.M., 2010. How Does Explicit Prioritization Alter Walking During Dual-Task Performance? Effects of Age and Sex on Gait Speed and Variability. *Physical therapy*, 90(2), pp.177–186.

Yogev- Seligmann, G., Hausdorff, J.M. and Giladi, N., 2012. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Movement disorders*, 27(6), pp.765–770.

Zaehle, T., Sandmann, P., Thorne, J., Jancke, L. and Herrmann, C., 2011. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. *BMC neuroscience*, 12(1), p.2.

Zakzanis, K.K., Mraz, R. and Graham, S.J., 2005. An fMRI study of the Trail Making Test. *Neuropsychologia*, 43(13), pp.1878–86.

Zhou, J., Hao, Y., Wang, Y., Jor'dan, A., Pascual-Leone, A., Zhang, J., Fang, J. and Manor, B., 2014. Transcranial direct current stimulation reduces the cost of performing a cognitive task on gait and postural control. *European Journal of Neuroscience*, 39(8), pp.1343–1348.

Ziemann, U., Rothwell, J.C. and Ridding, M.C., 1996. Interaction between intracortical inhibition and facilitation in human motor cortex. *The Journal of physiology*, 496 (Pt 3, pp.873–81.

Participant consent:

Please tick appropriate box

	YES	NO
Have you read the Research Participant Information Sheet?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Have you received satisfactory answers to all your questions?	☐	☐

Who have you spoken to?……………………………………………………………..

	YES	NO
Do you understand that you will not be referred to by name in any report concerning the study?	☐	☐

Do you understand that you are free to withdraw from the study:

at any time without having to give a reason for withdrawing? ☐ ☐

Do you agree to take part in this study? ☐ ☐

Please read the below statements fully, and sign below to confirm you have read and understood them.

I have read this form carefully and I fully understand the test procedure that will be performed and the associated risks and discomforts. I understand that all concerned will treat any information about myself that I have given, or that is obtained during the course of the tests, as confidential and that any data collected during the study will remain anonymous (subjects identifiable by number) and stored on a secure computer, locked by passwords only known by the investigator. I consent to participate in the test.

______________________________	______________________________
Date	Signature of subject
______________________________	______________________________
Date	Signature of investigator