The fine-tuning network:

an investigation into the neural correlates of

gait cycle adjustment and adaptation to split belt treadmill locomotion.

Dorelle Clare Hinton

Department of Kinesiology and Physical Education

McGill University, Montreal

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Contents

Abstract

Rationale: Previous literature has shown healthy adults are capable of quickly adapting and adjusting their gait pattern to the constraints of their environment. For instance, in a laboratory, a healthy adult can adjust and adapt their walking pattern to walk on a split belt treadmill, where each leg is driven at a different speed. The neural control underlying this process is hypothesized to require widespread use of brain networks and is under continuing investigation. Furthermore, our understanding of how neurodegeneration due to Parkinson's disease (PD) affects this automatic control of walking and gait alterations is emerging. The identification of the brain region(s) and network(s) required for gait adaptation and adjustments in healthy adults is essential before the neural changes due to PD can be fully understood.

Objective: My doctoral work aims to identify the underlying neural mechanisms in the control of gait adaptation and adjustments to the split belt treadmill using dual-task and positron emission tomography (PET) imaging methodologies in healthy adults and adults with PD.

Study 1 (Chapter 3): Here, a full systematic review of the current split belt treadmill literature was preformed to consolidate what is known about how the human central nervous system (CNS) controls adaptation to this type of symmetry perturbation. Based on the 61 studies identified, the initial gait adjustments to split belt walking is reliant on proprioceptive feedback to inform central pattern generators to modify lower limb muscle activation patterns appropriately while proprioceptive and visual feedback informs supraspinal centres for motor planning and motor output to adapt and store a new and efficient gait pattern to walk on belts at different speeds. Finally, evidence from participants with brain injury (post-stroke, cerebellar lesions) suggest that injury impedes, but does not completely take away, the ability to adjust and adapt aspects of the

gait pattern to split belts. Based on this evidence, a model was hypothesized for how the human CNS controls these different aspects of the full adaptation process.

Study 2 (Chapter 4): To further explore this model for split belt adaptation, a secondary cognitive task was used to assess whether split belt adaptation in young healthy adults, and the ensuing aftereffects, are altered by dual tasking. Further evidence of executive cognitive influence was found in the split belt adaptation process as participants prioritized split belt adaptation over the cognitive task, and in doing so, cognitive task accuracy was reduced. From this work, the early portion of split belt treadmill adaptation was found to be a cognitive interference period. For this reason, in our next study, a protocol was designed where participants recreated the initial adjustment period to asymmetric split belts on a continuous basis.

Study 3 (Chapter 5): Using PET imaging, areas of the young healthy brain that increase and decrease in activation when continuous adjustments to the gait cycle occur were identified. Continuous gait adjustments were associated with increased activity of supplementary motor areas (SMA), posterior parietal cortex (PPC), anterior cingulate cortex and anterior lateral cerebellum, and decreased activity of posterior cingulate and medial prefrontal cortex. From these results a "fine-tuning" network for human locomotion was proposed to exist which includes brain areas for sensorimotor integration, motor planning and goal directed attention. These findings suggest that distinct regions govern the inherent flexibility of the human locomotor plan to maintain a successful and adjustable walking pattern.

Study 4 (Chapter 6): The final study was set out to determine whether the presence of PD would affect the areas of activation within the "fine-tuning" network proposed in young healthy adults. During continuous belt speed changes adults with PD increased supplementary and primary motor area, PPC, posterior cingulate and right and left cerebellum (lobule I-IV) compared to typical

treadmill walking. In addition, adults with PD had a cluster of significantly greater activation within the premotor, supplementary and primary motor areas compared to healthy older adults. These findings are further support of the "fine tuning" network proposed in Study 3 and suggest that adults with PD are more reliant on proprioceptive feedback to adjust their gait pattern than healthy older adults.

Conclusions: From this thesis work we have been able to inform our understanding of the neural control of complex walking adjustments from one step to the next. Understanding how this model is used both in a young healthy CNS as well as one where cortical or subcortical resources are challenged, allows us to better understand how the CNS itself adapts to maintain locomotor performance.

Résumé

Fondement: La littérature démontre que les adultes en bonne santé sont capables d'adapter rapidement leur patron de marche aux contraintes environnementales. Par exemple, dans un laboratoire, un adulte en bonne santé peut ajuster et adapter son patron de marche à un tapis roulant à double courroies où chaque jambe est conduite à une vitesse différente. Les mécanismes neuronaux sous-jacents à ce processus nécessitent une utilisation généralisée des réseaux cérébraux qui demeurent peu compris. Toutefois, de plus en plus d'études concernant la façon dont la neurodégénération causée par la maladie Parkinson (MP) affecte ce contrôle automatique et les ajustements de la marche voient le jour. Pour que les changements neuronaux dus à la MP soient pleinement compris, il est nécessaire d'identifier les régions et les réseaux cérébraux nécessaires pour la locomotion complexe chez des adultes en bonne santé.

Objectif: Mon travail de doctorat vise à identifier les mécanismes neuronaux sous-jacents au contrôle de la marche automatique et à l'adaptation de la marche en utilisant des méthodologies de double tâches et d'imagerie tomographique par émission de positrons (TEP).

Étude 1 (Chapitre 3): Une revue systématique complète a été effectuée de la littérature actuelle au sujet du tapis roulant à double courroies pour consolider ce qui est connu sur la façon dont le système nerveux central (SNC) humain contrôle l'adaptation à ce type de perturbation de symétrie. Selon les 61 études identifiées, les ajustements initiaux à la marche avec double courroies dépendent du feedback proprioceptif qui informe les générateurs de schémas centraux de la nécessité de modifier les schémas d'activation musculaires des membres inférieurs de manière appropriée. D'autre part, les feedbacks proprioceptif et visuel informent les centres supra spinaux de la planification motrice et de la puissance motrice pour adapter et conserver un nouveau modèle

de marche efficace pour la marche sur tapis roulant à double courroies. Enfin, les données des participants souffrant de lésions cérébrales (post-AVC, lésions cérébelleuses) suggèrent que les blessures entravent, mais ne suppriment pas complètement, la capacité d'ajuster et d'adapter certains aspects de la marche sur tapis roulant à double courroies. Sur la base de ces preuves, un modèle a été proposé sur la façon dont le système nerveux central humain contrôle ces différents aspects du processus d'adaptation complet.

Étude 2 (Chapitre 4): Pour explorer davantage ce modèle d'adaptation aux doubles courroies, une tâche cognitive secondaire a été utilisée afin d'évaluer si l'adaptation à ce type de marche chez les jeunes adultes en santé est modifiée par une double tâche. Les résultats amènent d'autres preuves de l'influence cognitive de l'exécutif dans le processus d'adaptation aux doubles courroies. En effet, les participants semblent avoir priorisé l'adaptation à la tâche cognitive en réduisant leur précision à la tâche cognitive. La première partie de l'adaptation au tapis roulant avec double courroies est serait donc une période d'interférence cognitive. Pour cette raison, dans la prochaine étude, un protocole a été élaboré dans lequel les participants ont recréé la période d'ajustement initiale aux double courroies asymétriques de façon continue.

Étude 3 (Chapitre 5): À l'aide de l'imagerie TEP, nous avons identifié des régions cérébrales spécifiques qui augmentent ou diminuent en activation lors d'ajustements continus du cycle de marche chez des participants jeunes et en bonne santé. Ces ajustements continus de la marche ont été associés à une activité accrue de l'aire motrice supplémentaire, du cortex pariétal postérieur, du cortex cingulaire antérieur et du cervelet latéral antérieur, et à une diminution de l'activité du cingulaire postérieur et du cortex préfrontal médial. À partir de ces résultats, un réseau de « peaufinage » a été proposé pour la locomotion humaine. Ce dernier comprendrait des régions du cerveau responsables de l'intégration sensorimotrice, de la planification motrice et de l'attention

dirigée. Ces résultats suggèrent que des régions distinctes régissent à la flexibilité inhérente qu'a le plan locomoteur humain dans le but de maintenir un modèle de marche ajustable et fonctionnel.

Étude 4 (Chapitre 6): La dernière étude visait à déterminer si la présence de la MP affecterait les régions d'activation au sein du réseau de « peaufinage » proposé chez les jeunes adultes en bonne santé. Chez les adultes atteints de la MP, l'activité de l'aire motrice supplémentaire, du cortex moteur primaire, du cortex pariétal postérieur, du cortex cingulaire postérieur et du cervelet droit et gauche (lobule I-IV), lors des changements continus de vitesse des courroies, a augmenté, ce qui n'était pas le cas lors de la marche sur tapis roulant typique. De plus, les adultes atteints de la MP présentaient une zone d'activation significativement plus importante dans les régions motrices, prémotrices, supplémentaires et motrices primaire que les adultes plus âgés en bonne santé. Ces résultats viennent appuyer le réseau de « peaufinage » proposé dans l'étude 3.

Conclusions: À partir de cette thèse, nous avons pu éclairer la compréhension que nous avons du contrôle neuronal des ajustements de la marche complexe d'une étape à l'autre. Comprendre comment ce modèle est utilisé, à la fois dans une jeune SNC saine et dans un contexte où les ressources corticales ou sous-corticales sont mises à l'épreuve, nous permet de mieux comprendre comment le SNC lui-même s'adapte pour maintenir les performances locomotrices.

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Contribution to Original Research

This thesis was prepared according to McGill University's regulations for a manuscript-based thesis. It consists of four manuscripts (2 published, 1 under review for publication, 1 in preparation for submission).

Chapter 1 includes a brief introduction to the study of gait adaptation and the specifics aims and objectives of this thesis.

Chapter 2 provides a comprehensive review of literature important to the understanding of the neural correlates of gait adaptation. In this chapter, the biomechanical changes to gait on the split belt treadmill are discussed, the understood neural correlates of human walking are summarized, and finally, the methods to assess the neural correlates of walking using dual tasking, positron emission tomography imaging and by assessing the changes to control of walking that occur with Parkinson's disease are summarized.

Chapters 3 -6 include the manuscripts for each of the 4 thesis studies. Each chapter includes title page, abstract, introduction, methods, results with tables and figures, discussion, and references specific to the manuscript. A preface has been included between each manuscript chapter.

Chapter 3 consists of a manuscript entitled "*Understanding human neural control of gait adaptation to the split belt treadmill: A systematic review*".

Originality: This was the first systematic review to evaluate the neural control of human gait adaptation to the split belt treadmill. This manuscript is currently under review at *Neuroscience* (NSC-20-0136).

Chapter 4 consists of a manuscript entitled "*Does dual task placement or duration affect split belt treadmill adaptation?*".

Originality: This dual-task study sought to better understand the cognitive overlap between split belt treadmill adaptation and a working memory task at different points in the adaptation process. This manuscript was published in *Gait & Posture* (Hinton, Conradsson et al. 2020). Based on the permissions granted to Elsevier journal authors, this article has been included as part of this thesis for non-commercial purposes.

Chapter 5 consists of a manuscript entitled "*Adjusting gait step-by-step: Brain activation during split belt treadmill walking*".

Originality: This imaging study was the first to utilize ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) PET imaging to assess glucose metabolism of the brain during split belt treadmill walking in young healthy adults. This manuscript was published in *Neuroimage* (Hinton, Thiel et al. 2019). Based on the permissions granted to Elsevier journal authors, this article has been included as part of this thesis for non-commercial purposes.

Chapter 6 consists of a manuscript entitled "*Parkinson's disease affects neural activation during continuous gait alterations to the split belt treadmill: An [^{18}F]-FDG PET Study*".

Originality: This imaging study expands on the study presented in Chapter 5 and utilized ^{18}F-FDG PET imaging to assess glucose metabolism of the brain during split belt treadmill walking in healthy older adults and adults with Parkinson's disease. This is the first study to broaden the "Fine-Tuning Network" proposed in Chapter 5 to understand the effects of PD in step-by-step adjustments. This manuscript is in preparation to be submitted for publication.

Chapter 7 consists of a general discussion and summary of the overall thesis.

Contribution of Authors

This thesis consists of four original research projects that I, Dorelle C. Hinton, completed under the supervision of Dr. Caroline Paquette. The following describes the input and contribution to the work from the co-authors named on the title page of each manuscript.

For **Study 1** (Chapter 3 entitled *"Understanding human neural control of gait adaptation to the split belt treadmill: A systematic review"*), I determined the review criteria; generated the objective and hypothesis for the study; collected and analysed the data; and lastly wrote and revised the manuscript with input and feedback from my supervisor and co-author.

For **Study 2** (Chapter 4 entitled *"Does dual task placement or duration affect split belt treadmill adaptation?"*), I designed the study protocol; generated the objective and hypotheses for the study; recruited study participants; collected and analyzed data; and finally wrote and revised the manuscript with critical input and feedback from my supervisor and co-authors.

For **Study 3** (Chapter 5 entitled *"Adjusting gait step-by-step: Brain activation during split belt treadmill walking"*), I designed the study protocol; generated the objective and hypotheses for the study; recruited study participants; collected and analyzed data; and finally wrote and revised the manuscript with critical input and feedback from my supervisor and co-authors.

For **Study 4** (Chapter 6 entitled "*Parkinson's disease affects neural activation during continuous gait alterations to the split belt treadmill: An [18F] FDG PET Study*"), I designed the study protocol; generated the objective and hypotheses for the study; recruited study participants; collected and analyzed data; and finally wrote and revised the manuscript with critical input and feedback from my supervisor and co-authors.

Dr. Caroline Paquette was the principle investigator on Studies 1-4 and oversaw all aspects including: study conceptualization, study design, ethics approval from the Research Institute of McGill University and Montreal Neurological Institute (MNI), data analysis and interpretation, and content of all manuscripts included in this thesis.

Dr. David Conradsson was a fellow member of the Human Brain Control of Locomotion Lab as a postdoctoral fellow also under the supervision of Dr. Caroline Paquette. He participated in the review design in Study 1, the data analysis in Study 2 and provided critical feedback on the manuscripts for Studies 1 and 2.

Dr. Laurent Bouyer was a member of my thesis advisory committee. Dr. Bouyer contributed to the protocol design of Studies 2 and 3 and provided critical feedback on the manuscript for Studies 2 and 3.

Dr. Alexander Thiel was a member of my thesis advisory committee. Dr. Thiel provided critical feedback on the manuscript for Study 3 and contributed to the theoretical background and PET imaging procedures in Study 3 and 4.

Dr. Jean-Paul Soucy is the director of the Positron Emission Tomography Unit at the MNI and provided critical feedback on the manuscript for Study 3 and contributed to the theoretical background and PET imaging procedures in Study 3 and 4.

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Chapter 1: Introduction

1.1 Thesis Rationale

Healthy adults have the ability to alter, adjust and adapt the way we walk to our surroundings easily and without having to "think" about what we are doing. While these gait changes seem to occur quickly, and almost automatically, in a healthy nervous system, a broad network of brain regions is involved. Furthermore, with a neurodegenerative disease, such as Parkinson's disease (PD), the network of brain areas involved may be altered and these types of step-to-step adjustments can become more difficult. In order to assess the ability to adapt the gait cycle in the laboratory, a split belt treadmill can be used. This treadmill, with independent belts under each foot, allows for each leg to be driven at a different speed at the same time. In this type of paradigm, we can test and assess how the human central nervous system (CNS) adjusts and adapts the walking pattern to asymmetric walking. In my doctoral work, I sought to identify the network of brain areas that are responsible for, and contribute to, this inherent ability to "fine-tune" our walking pattern from one step to the next. I did this using 3 different methodologies: (1) a systematic review of the current literature assessing split belt treadmill walking; (2) walking while completing a secondary cognitive task; and (3) brain imaging using positron emission tomography (PET) to analyze changes in brain metabolism during split belt treadmill walking. The work presented within this thesis advances our understanding of the specific brain networks underlying our inherent ability to adjust the way we walk efficiently to our surroundings. Identification of the brain region(s) and network(s) required for complex locomotion in healthy adults is essential before the neural changes due to normal aging and pathologies (e.g. Parkinson's disease) can be fully understood.

1.2 Thesis Objectives

1. Consolidate the current hypotheses for the neural control of gait adaptation to the split belt treadmill in the human central nervous system (Research Question #1). By completing a systematic review of the split belt treadmill adaptation literature, a model for the distinct roles of the CNS in adapting human gait to the split belt treadmill will be proposed.

2. Identify the cognitive influence on gait adaptation to split belt treadmill and the shared neural substrates between a working memory task and split belt treadmill adaptation in young healthy adults (Research Question #2 and #2a). Using dual-task methodologies, the relative change in cognitive input to carry out locomotor adaptation will be estimated.

3. Identify the neural correlates of gait adjustments to the split belt treadmill healthy young adults (Research Question #3). Using neuroimaging analysis, the network of brain areas activated to adjust the gait cycle to walk on the split belt treadmill will be identified. Comparisons to typical treadmill walking will be made to identify areas specific to complex locomotion and a *Fine-Tuning Network* for adjusting the gait cycle from one step to the next will be proposed.

4. Identify the neural correlates of gait adjustments to the split belt treadmill in adults with Parkinson's disease (Research Question #4). Using neuroimaging analysis, the network of brain areas activated to adjust the gait cycle to walk on the split belt treadmill will be identified in healthy older adults and adults with PD. Comparisons to typical treadmill walking will be made to identify areas specific to complex locomotion. The proposed *Fine-Tuning Network* will be expanded to include changes that occur with Parkinson's disease.

1.3 Research Questions

1. What major hypotheses for the neural correlates of split belt treadmill adaptation exist in the literature? (Chapter 3)
2. Does split belt treadmill walking require increased cognitive compared to tied-belt treadmill walking? (Chapter 4)
    a. Do the cognitive requirements of split belt treadmill change over the course of split belt treadmill adaptation? (Chapter 4)
3. What network of brain areas are required for adjusting the gait cycle to split belt treadmill walking in healthy young adults? (Chapter 5)
4. What areas of the brain are required for adjusting the gait cycle to split belt treadmill walking in healthy older adults and adults with Parkinson's disease? (Chapter 6)
    a. How do these networks influence our understanding of the *Fine-Tuning Network* proposed for healthy young adults? (Chapter 6)

1.4 Thesis Implications

1. The cognitive control of walking on asymmetric belts will be confirmed.
2. A model for the control of split belt treadmill walking in healthy young adults will be proposed based on a review of current literature and neuroimaging analysis during split belt treadmill walking.
3. The proposed model will be tested and expanded to include the influence of Parkinson's disease based on neuroimaging analysis during split belt treadmill walking.

Chapter 2: Literature Review

A typical day for a healthy adult will likely include walking around their home or place of work, walking to and from their car or the bus stop, or walking down the street on the way to a store. The incredible aspect of these seemingly inconsequential day-to-day actions is our inherent capability to walk without truly *thinking* about how we are moving from one step to the next. The human central nervous system employs a variety of controls to ensure that we can create walking patterns appropriate to a wide variety of scenarios and situations. Walking is rarely straight or symmetrical. We turn around corners, avoid obstacles such as puddles on the sidewalk or a child's toy in the hallway, and steer around other pedestrians in a crowd. How is it that the human brain and spinal cord can accommodate these changes to our walking pattern, sometimes even when previously unplanned? The research interests of this doctoral work lie in understanding the brain networks in command of adjusting locomotor control from one step to the next.

2.1 Gait Biomechanics of Locomotor Adaptation to the Split belt Treadmill

A diverse set of walking patterns, with alterations to both spatial (e.g. step length) and temporal (e.g. dual support timing) aspects of gait, are required to navigate our environment. In the laboratory, a split belt treadmill, with independently driven belts beneath each foot, allows for the study of gait adaptation to asymmetric belt speeds. Treadmill belts are separated by a small gap and participants place one foot on each and walk as they might on a typical treadmill. Belts can either be driven at the same speed, known as a "tied-belt" condition, that is used to simulate typical treadmill walking where only one belt exists. Or, belts can be driven at different speeds, known as a "split belt" condition. Use of the split belt condition has allowed for the study of gait

changes to short rapid changes to belt speeds, or with extended exposure, the study of gait adaptation.

Alteration to an already familiar motor plan, better known as motor adaptation, is required to respond to ongoing challenges in our daily environment. Motor adaptation is inherent to a healthy neural system, but can be rendered less efficient by brain injury, disease or aging. The ability to properly adapt is important for gait tasks, so that cognitive and energetic resources are not spent navigating each step. Locomotor adaptation reorganizes or updates an internal sensorimotor map in order to anticipate and apply a newly learned locomotor pattern to a perturbed or altered context (Reisman, Block et al. 2005, Reisman, Bastian et al. 2010, Malone, Vasudevan et al. 2011, Blanchette, Moffet et al. 2012). While new motor skill acquisition is a feedback and error driven process of acquiring a new muscle activation pattern based on the current environment, motor adaptation anticipates the most efficient locomotor pattern for the environment (Reisman, Block et al. 2005, Reisman, Bastian et al. 2010, Malone, Vasudevan et al. 2011, Blanchette, Moffet et al. 2012). These anticipatory changes provide flexibility and retain a sense of locomotor automaticity across a variety of settings and environments (Reisman, Bastian et al. 2010).

Typically, after a baseline period of normal treadmill walking, participants require an adaptation period to walk successfully with the addition of the perturbation. Initially, when participants first experience the split belt treadmill, their gait pattern is temporarily changed to their well-established, permanent walking pattern and typically presents as a large limp. However, with extended exposure to split belts, adaptation allows the motor system to detect the perturbation more efficiently than simply reacting to the environment reflexively with each step (Reisman, Bastian et al. 2010). Healthy populations achieve adaptation, demonstrated through gait symmetry

or a balanced walking pattern from one step to the next, within minutes (Dietz, Zijlstra et al. 1994, Prokop, Berger et al. 1995, Jensen, Prokop et al. 1998, Malone and Bastian 2010). Once the perturbation is removed, asymmetric gait is present during a de-adaptation phase until the motor system can re-adapt to symmetry. Even though symmetry perturbations do not always affect gait in the same ways, common conclusions have been made across paradigms. These conclusions can be classified based on the timing of initial gait changes, the permanence and longevity of the gait pattern changes and the hypothesized neural location of control.

Feedback- and feedforward-driven adaptations to the split belt treadmill

Initially, feedback-driven or spontaneous changes to gait in response to a symmetry perturbation are focused on maintaining stability and upright posture. Motivated by sensorimotor feedback information from the periphery, such as the belt speed and/or muscle and joint position alterations, cause immediate changes to gait through intralimb variables, namely stride length and time spent in stance phase (Reisman, Block et al. 2005, Lam, Anderschitz et al. 2006, Morton and Bastian 2006, Choi, Vining et al. 2009, Reisman, Bastian et al. 2010). Feedback-driven changes are the locomotor pattern changes that can be seen within three to five steps of a symmetry perturbation such as an elastic resistance on one leg or walking on split belts (Reisman, Block et al. 2005, Lam, Anderschitz et al. 2006, Blanchette and Bouyer 2009). Evidence suggests feedback driven alterations to the gait pattern stem from a safety response. Aspects of the gait cycle required for safe and stable locomotion are amplified, such as preparation for a stable heel contact (Lam, Anderschitz et al. 2006, Noble and Prentice 2006, Blanchette and Bouyer 2009). Interestingly, even when participants can expect the type of perturbation, such as resistance to the stance phase with an elastic force field, changes to the gait cycle still occur and must be counteracted through immediate feedback-driven changes to maintain stability (Noble and Prentice 2006, Blanchette

and Bouyer 2009). This can come in the form of changing foot swing velocity, altering stride length or adjusting time spent in stance and/or swing. Feedback drive adaptation to gait are not affected with cerebellar damage (Morton and Bastian 2006) or hemispherectomy (Choi, Vining et al. 2009) indicating its neural control may be at the spinal cord level.

In contrast to the immediate feedback-driven, safety-based changes, a more slowly adapting progressive shift in gait behavior is also observed in response to a symmetry perturbation (Noble and Prentice 2006). Over the course of adaptation, there is a gradual transfer from feedback-driven gait changes to feedforward anticipatory pattern alterations, creating a newly learned, context-specific locomotor program with reduced errors (Reisman, Bastian et al. 2010, Blanchette, Moffet et al. 2012). Feedforward-driven adaptations are anticipatory changes that integrate sensorimotor information to update the motor plan to a prolonged perturbation (Reisman, Block et al. 2005, Morton and Bastian 2006, Choi, Vining et al. 2009, Reisman, Bastian et al. 2010). Primarily focused on interlimb coordination, feedforward-driven changes aid in recalibration of new steady-state pattern, rather than the initial feedback-driven intralimb joint stiffness (Noble and Prentice 2006, Blanchette and Bouyer 2009, Barthelemy, Alain et al. 2012). For instance, in response to the perturbation, initially, muscle activations are constantly elevated and inefficient. Feedforward adaptations return muscle activations to burst-like activity, decreasing negative work and aiding in decreased metabolic costs (Gordon and Ferris 2007). Gait parameters involved in interlimb coordination such as step length, time spent in double support, and interlimb phasing show more gradual adaptations to symmetry perturbations. That is to say these gait parameters are altered through feedforward anticipations to the destabilizing forces experienced during swing phase (Reisman, Block et al. 2005, Lam, Anderschitz et al. 2006, Morton and Bastian 2006, Choi, Vining et al. 2009). While healthy controls are able to make these

anticipatory changes to interlimb coordination relatively easily, patients with cerebellar damage cannot, indicating the possibility that cortical input may be involved in this process (Morton and Bastian 2006).

Given that both intralimb and interlimb coordination are adapted with unilateral perturbations to gait, a strong neural coupling exists between legs (Reisman, Bastian et al. 2010). Although the optimal neural signal would be to duplicate the same signal to both legs, asymmetric perturbations provide evidence that the central nervous system is able to send unique signals for the movement and placement of each leg separately (Noble and Prentice 2006). At first, a similar response to the symmetry perturbation is present in both legs indicating a common post-adaptation pattern. Notably, reciprocal muscle activation is immediately present to produce a 1:1 ratio for foot placement. These feedback-driven adaptation circuits are hypothesized to stem from a lower level set of neural activation patterns, not requiring active cortical input (Reisman, Block et al. 2005, Noble and Prentice 2006). These circuits are independently controlled from circuits responsible for interlimb coordination required to reach symmetric, stable walking. As such, interlimb coordination does not necessitate altering intralimb coordination (Reisman, Block et al. 2005).

Feedforward-driven adaptations are geared towards increasing peak positive power and decreasing peak negative power and shifting away from muscle activations that are not advantageous to the circumstances (Gordon and Ferris 2007). Interestingly, this adapted pattern is one which minimizes movement costs in the perturbed environment, not necessarily one that completely counteracts performance errors, and may not be the same as the one used in the typical environment (Blanchette and Bouyer 2009, Choi, Vining et al. 2009). It is also apparent that different phases of the gait cycle use different types of information to adapt to symmetry

perturbations. While immediate feedback-driven changes are recognized during late swing phase and in preparation for heel contact, changes to muscle activations just prior to toe off and during early swing are later to adapt and reliant on feedforward-driven adaptations. (Lam, Anderschitz et al. 2006, Blanchette and Bouyer 2009, Fortin, Blanchette et al. 2009).

Why would it be important for the central nervous system to go beyond feedback-driven adaptation to adapt interlimb coordination? Inherently, symmetric walking is more stable and more efficient, decreasing the metabolic costs of walking. Given that all participants across all studies mentioned maintained a 1:1 ratio for foot placement, the neural system for interlimb coupling is biased towards symmetry. As such, it adapts weight transfer from one leg to the other via interlimb phasing and orientation (Reisman, Block et al. 2005, Morton and Bastian 2006). Evidence from symmetry perturbations to gait also suggests that spatial and temporal aspects of gait are adapted separately. These would also indicate that spatial measures, such as step length are not neurally controlled in the same way as temporal measures such as limb phasing and time spent in double support (Choi, Vining et al. 2009, Malone, Vasudevan et al. 2011). This is further evidenced by pathologies, such as hemispherectomy patients who show evidence of spatial adaptation (i.e. adaptation of step length) but no adaptation to the temporal aspects of their gait (Choi, Vining et al. 2009). Interestingly, hemispherectomy patients had baseline temporal asymmetry but no spatial asymmetry presents during baseline, typical walking. This could also indicate that the nervous system is better equipped at re-establishing spatial aspects of gait. The temporal aspects of gait may be more complex to alter and under cortical rather than spinal control (Choi, Vining et al. 2009).

Short-term storage induced by split belt treadmill adaptation

Through anticipatory changes to the gait pattern, the expected effect of the perturbation is incorporated into planning. Consequently, when the perturbation is removed (i.e. the environment returns to the original setting) motor errors, known as aftereffects, are present. Even though the environment is the typical environment expected for walking in terms of surface and external forces, and the previously newly learned pattern must be unlearned (Blanchette and Bouyer 2009, Choi, Vining et al. 2009). The existence of aftereffects indicate that feedforward-driven adaptations and storage of the newly adapted pattern have occurred through central recalibration of an Internal Model for locomotor pattern generation (Lam, Anderschitz et al. 2006, Morton and Bastian 2006, Gordon and Ferris 2007, Blanchette and Bouyer 2009, Fortin, Blanchette et al. 2009, Reisman, Bastian et al. 2010, Blanchette, Moffet et al. 2012). Gait changes brought on through feedforward-driven changes have the longest standing aftereffects (Lam, Anderschitz et al. 2006, Fortin, Blanchette et al. 2009).

The presence of aftereffects in healthy adult participants can be seen after as little as three steps in the perturbed environment, indicating that predictive strategies are already present in the anticipation of force changes (Lam, Anderschitz et al. 2006). Evidence suggests the transfer of the adapted motor pattern is better with an extended adaptation period as the size and duration of aftereffects and the duration of the adaptation period are related (Fortin, Blanchette et al. 2009). The duration of the aftereffects is relative to the recalibration effect which increases as the number of strides spent in the perturbation period increases (Fortin, Blanchette et al. 2009, Choi, Bouyer et al. 2015). Notably, the absolute perturbation size (i.e. the difference in perturbation to each leg) affects the magnitude of the aftereffects, indicating the central nervous system is able to gauge the force intensity produced by the perturbation and adjust accordingly (Fortin, Blanchette et al. 2009).

Aftereffects also persist when there is a delay between adaptation to the perturbation and the return to the typical environment. Consequently, this means that participants are aware when the change back to the original setting will occur, further establishing the central nature of the motor plan recalibration (Blanchette and Bouyer 2009, Fortin, Blanchette et al. 2009). Conversely, where aftereffects are not present, such as in patients with cerebellar damage, storage of the adapted pattern does not occur and any gait changes are thought to be based only on sensorimotor feedback (Morton and Bastian 2006).

The *Internal Model Theory* postulates that the central nervous system maintains a representation of the dynamics of each limb and a learned association between the movement instructions, actions, and outcomes (Noble and Prentice 2006, Gordon and Ferris 2007). This Internal Model is the basis for current and upcoming motor programs and is updated with experience (Lam, Anderschitz et al. 2006, Noble and Prentice 2006, Gordon and Ferris 2007). In the symmetry perturbation scenario, the central nervous system is instructed to update the Internal Model based on the perturbation. As a result, the motor commands for locomotion are updated, the resulting motor patterns are optimized to the perturbed environment and are stored and retained. Importantly, the alterations to the gait pattern plan are context specific, and storage is separate from the original, more permanent or automatic pattern (Gordon and Ferris 2007, Fortin, Blanchette et al. 2009). When healthy participants switch back to the typical environment, aftereffects are immediately present for a short time, however the Internal Model will detect error between the planned movements and the actual movement outcome and will revert back to the more automatic gait pattern.

Summary

Across a variety of human participants groups, the gait pattern continues its stepping pattern by making similar changes to the gait cycle. For instance, to properly adjust the gait cycle to split belts, participants will increase time spent in stance on the slower moving belt and decrease time spent in stance on the faster moving belt. These characteristic changes to gait biomechanics upon exposure to split belts provide indications of an underlying network for the neural control of gait adjustments and adaptation. This thesis will utilize changes to gait biomechanics, in parallel with techniques to quantify neural control, to make observations about this underlying neural control of gait adjustments and adaptations.

2.2 The Neural Control of Walking

Imaging studies of human locomotion have identified a wide range of cortical, subcortical and cerebellar activity associated with steady-state walking. These areas of increased activity range from primary motor and sensorimotor cortical areas (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999, Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2004, Mihara, Miyai et al. 2007, Suzuki, Miyai et al. 2008, Gwin, Gramann et al. 2011, Shimada, Ishii et al. 2013), to occipital lobe (la Fougere, Zwergal et al. 2010, Shimada, Ishii et al. 2013) and visual cortex (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999), to anterior cingulate (Hanakawa, Katsumi et al. 1999) and parietal cortices (Hanakawa, Katsumi et al. 1999, Gwin, Gramann et al. 2011) and temporal (Fukuyama, Ouchi et al. 1997) and para hippocampal lobes (la Fougere, Zwergal et al. 2010). Subcortically, increased activation has been noted in the basal ganglia (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999, Ouchi, Kanno et al. 2001), pons (Hanakawa, Katsumi

et al. 1999) and finally the cerebellum (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999, la Fougere, Zwergal et al. 2010, Shimada, Ishii et al. 2013). Of note, most widespread activations noted were relative to lying down, so aspects of upright postural control optic flow and auditory environmental cues are also be included in this activity.

The base model on which this doctoral work is expanding, is the executive neural control of walking proposed by la Fougere and colleagues (2010; Figure 2.1). To create this initial model, they compared brain activity during walking using positron emission tomography (PET) imaging to imagined walking using functional magnetic resonance imaging (fMRI). They proposed that steady-state walking, without planned changes to the step-to-step walking pattern, would require activity from the primary motor cortex, but that this information would be directly relayed to central pattern generator (CPGs) in the spinal cord (la Fougere, Zwergal et al. 2010). This loop would bypass subcortical structures such as the basal ganglia and brainstem and instead rely on feedback from the spinal cord to be relayed through the cerebellum back to the primary motor cortex via the thalamus. This direct pathway for straight, steady-state walking allows cognitive resources to be available for other ongoing tasks.

In the case of planned changes to the walking pattern, these anticipatory changes to the gait pattern occur as a result of a change in the motor plan from repeated exposure to the reactive gait changes with the goal of minimizing errors. Expanding on their executive network, la Fougere and colleagues (2010) hypothesized that this error driven feedback would originate from the spinal cord, through cerebellum to brainstem and basal ganglia, and would create a functional loop with the supplementary motor areas (SMA). This would allow for alterations to the ongoing motor plan through the brainstem and for updates to environmental constraints (la Fougere, Zwergal et al. 2010). This functional network for planned walking modifications has been confirmed with other

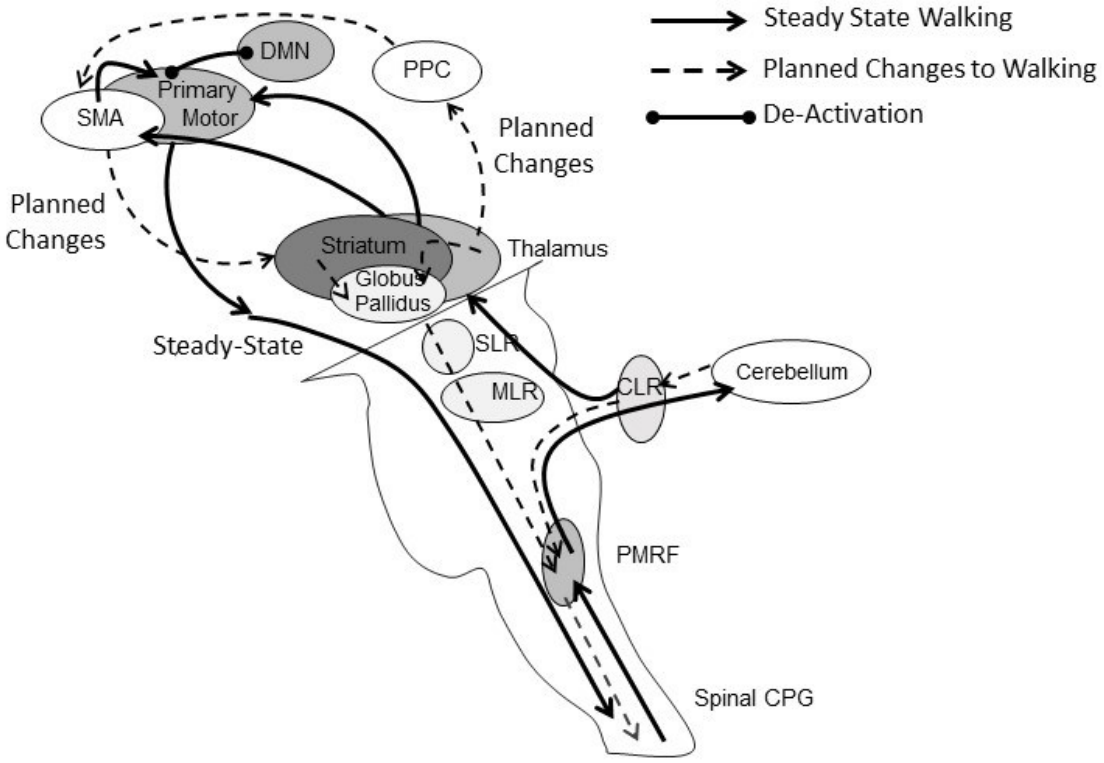

Figure 2.1 *Neural control of steady state walking and planned changes to the walking pattern (Adapted from la Fougere, Zwergal et al. 2010). Steady state walking utilizes direct sensorimotor feedback to inform the cerebellum and cortex of the ongoing motor plan. When changes to the walking pattern are necessary, input from the supplementary motor area (SMA) and posterior parietal cortex (PPC) will integrate ongoing sensorimotor feedback to successfully implement walking patter changes. Finally, during motor task execution, deactivation of the Default Mode Network (DMN) occurs.*

neuroimaging studies involving locomotion, suggesting that sensorimotor integration while walking would not only require cortical activation of SMA (Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008) but would also involve the posterior parietal cortex (PPC) (Lajoie, Andujar et al. 2010, Gwin, Gramann et al. 2011, Billington, Wilkie et al. 2013, Drew and Marigold 2015, Mitchell, Starrs et al. 2018, Wong and Lomber 2018) and primary motor and somatosensory areas

(Fukuyama, Ouchi et al. 1997, Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008, Gwin, Gramann et al. 2011). Finally, lateral cerebellar areas have been implicated in goal directed, or anticipatory, foot placement changes (Ilg, Giese et al. 2008) and adaptation of the gait pattern to split belt walking (Morton and Bastian 2006) while midline cerebellar lesions indicate that this region has a role in the dynamic postural control required during typical straight walking (Bastian, Mink et al. 1998). In addition to further cortical activation, the healthy CNS also reduces activity in areas known to be part of the Default Mode Network (DMN) during task performance (Raichle, MacLeod et al. 2001). The DMN is active at rest and involved in self-reference, memory and thought and deactivates when any motor tasks are performed including walking (Crockett, Hsu et al. 2017).

2.3 The Neural Control of Gait Adaptation

Given the wide range of cortical and subcortical areas involved in both typical steady-state walking and planned changes to the walking pattern, and in the absence of brain imaging studies examining split belt treadmill adaptation, there are a wide range of hypothesized regions in a healthy neural systems responsible for adapting to asymmetric gait quickly and efficiently. Given the difference in time course of adaptation and storage, it is clear that different neural structures are responsible for different aspects of gait adjustment and adaptation (Lam, Anderschitz et al. 2006, Morton and Bastian 2006). Based on evidence from patients with hemispherectomy (Choi, Vining et al. 2009) and cerebellar damage (Morton and Bastian 2006) it is hypothesized that the initial, fast adaptations to gait in response to a symmetry perturbation do not require higher-order cerebral mechanisms. Both patient populations can walk successfully on a split belt treadmill with their ability to maintain feedback-driven adaptations to gait. Aligning with the model in Figure

2.1, the brain stem and spinal circuits are responsible for maintaining postural tone and the reciprocal pattern of muscle activation required for basic locomotion (Morton and Bastian 2006, Reisman, Bastian et al. 2010). CPG's located within the spinal cord integrate sensory information from the periphery with the basic locomotor patterns generated in the brainstem (Noble and Prentice 2006). Previous work has highlighted the possibility that each leg is controlled by its own neuronal apparatus coupled with both peripheral proprioceptive receptors and spinal circuits (Dietz, Zijlstra et al. 1994, Prokop, Berger et al. 1995, Jensen, Prokop et al. 1998). As such, feedback-driven adaptations seen immediately post-symmetry perturbations are associated with these lower level neural structures (Reisman, Block et al. 2005, Noble and Prentice 2006, Choi, Vining et al. 2009, Reisman, Bastian et al. 2010).

Observed spatial changes to gait are perhaps an adaptation to actual ground conditions by the flexor muscles of the leg, particularly the gastrocnemius, responsible for counter-acting gravity (Dietz, Zijlstra et al. 1994). Given this evidence, it was hypothesized that the central responsibility for the leg flexor muscles is locomotion pace-making through proprioceptive modulation of the gastrocnemius (Dietz, Zijlstra et al. 1994). It was proposed that adaptation to distinct belt speeds between legs was possible via peripheral feedback from the gastrocnemius muscle, responsible for toe-off phase of the step cycle, to the spinal cord. This spinal circuit information then influences pre-programmed input to the tibialis anterior muscle, primarily involved in raising the toes for heel contact to occur (Dietz, Zijlstra et al. 1994). Using electromyography to quantify muscle activation, changes in activation were hypothesized to be goal-directed to compensate for the gait symmetry perturbation rather than to stiffen the system or increase stability (Prokop, Berger et al. 1995). In addition, load receptors influence the severity of a gait asymmetry and that load receptor input, indicating where most of body weight exists over top of foot, influences gait adaptation

(Jensen, Prokop et al. 1998). These findings confirmed an interaction between central mechanisms and proprioceptive feedback as the learning effect was leg-specific.

The motor cortex is concerned with the initial stages of motor learning (Choi, Bouyer et al. 2015). Although not particularly involved in unperturbed, typical, gait, it has been shown to be required for precise movements and limb control during locomotion. The motor cortex aids careful limb placement through control of activation level, duration and timing of small groups of synergistic muscles (Reisman, Bastian et al. 2010, Choi, Bouyer et al. 2015). It is well known that visuo-somatosensory-motor information integration is of utmost importance for the control and execution of complex gait (Barthelemy, Alain et al. 2012, Choi, Bouyer et al. 2015). Higher level cortical input from the primary sensory and motor areas and sensory association areas is required for feedback control in implementing a feedforward anticipatory change (Reisman, Block et al. 2005). This includes hip positioning and weight loading of the contralateral limb in the adaptation of the stance-swing transition. Evidence from hemispherectomy patients also implicates the motor cortex in limb timing during gait (Choi, Vining et al. 2009). The motor cortex, along with the cerebellum, aids in sensory prediction error, driving adaption through sensing differences in planned actions and actual execution (Choi, Vining et al. 2009, Barthelemy, Alain et al. 2012). Retention of adapted locomotor patterns is impaired in patients with large cortical lesions, signifying the importance of higher cerebral input in anticipatory locomotor adaptation and pattern storage (Choi, Vining et al. 2009, Choi, Bouyer et al. 2015).

By incorporating sensorimotor feedback of ongoing movements with the current Internal Model, the cerebellum aids in feedforward-driven gait adaptation (Reisman, Block et al. 2005, Morton and Bastian 2006, Reisman, Bastian et al. 2010). The cerebellum integrates sensorimotor feedback from the lower limb joints, muscles and proprioceptive receptors in order to compare the

intended leg movements with the actual resulting movements (Morton and Bastian 2006). Differences between the motor plan and actual execution, via a gait variable such as foot swing velocity, will provide corrections and updates to the Internal Model. The comparison of sensorimotor feedback at the cerebellar level is critical for implementing predictive changes. This has been quantified via cerebellum excitability modifications during split belt walking. The greatest change in cerebellum excitability occurred during early adaptation, indicating its necessity to adapt to a symmetry perturbation (Malone, Vasudevan et al. 2011). For this reason, damage to the cerebellum impeded patients' gait adaptability and storage of a newly learned motor pattern for anticipatory changes. Specifically, cerebellar damage patients were unable to adapt spatial parameters of gait but interestingly, temporal aspects of gait were kept intact (Choi, Vining et al. 2009). Cerebellar damage does not affect feedback-driven adaptations, therefore patients will be able to walk within the perturbed environment, but will be less likely to store a newly learned pattern and show aftereffects once returned to the typical walking environment (Morton and Bastian 2006, Reisman, Bastian et al. 2010). Malone and Bastian (2010) also present a plausible case that distinct cerebellar regions may be responsible for spatial and temporal locomotor control since a distraction task further exacerbated gait asymmetries beyond control group performance. The authors explain that if the cerebellum modifies spatial aspects of typical gait and explicit visual attention affects spatial asymmetries, then secondary visual cognitive demands would reveal these types of asymmetries, as was seen in this particular paradigm (Malone and Bastian 2010).

Corticospinal tract excitability changes are a consequence of adaptive changes induced by cerebellar activity. Modifications to corticospinal tract excitability are responsible for changing muscle activations (increasing or decreasing) in order to reduce overall movement error in the context of the perturbation (Malone, Vasudevan et al. 2011, Barthelemy, Alain et al. 2012).

Evidence suggests changes are specific to the gait task itself as they were only observed during walking with an elastic resistance (Malone, Vasudevan et al. 2011, Barthelemy, Alain et al. 2012). Finally, circuits between primary motor cortices and the cerebellum increase healthy participants' flexibility and to properly incorporate all sensorimotor feedback into updating the current Internal Model to the constraints of the current environment (Malone, Vasudevan et al. 2011).

Summary

Capturing human brain activity during a motor task, let alone locomotion, is difficult. Ideally, upright posture, independent balance control and full body range of motion are possible to capture the participant's typical walking behaviour while also assessing whole brain activity. This type of brain activity analysis is not yet fully available. Instead, we rely on combining different types of imaging analysis, testing scenarios, walking tasks and participant groups to best hypothesize how the brain controls the way we walk. This thesis utilizes three different protocols to assess supraspinal control of walking: dual tasking (Chapter 4), positron emission tomography imaging (Chapter 5, 6) and a clinical participant group (Chapter 6) to make conclusions about the neural control of gait adjustments and adaptation.

2.4 Assessing Supraspinal Control of Walking: Dual Task Methodology

The inability of a group of older adults to talk and walk simultaneously, was first published as anecdotal evidence that gait and postural control required cognition (Lundin-Olsson, Nyberg et al. 1997). Lundin-Olsson and colleagues (1997) observed that older adults would "stop walking when talking" as way to simplify the overall task of performing two things at once. Classic dual-task paradigms using a secondary executive function or attention task simultaneous to walking or

standing balance have explored the extent to which either cognitive and/or postural control performance declines due to interference between tasks (Woollacott and Shumway-Cook 2002, Fraizer and Mitra 2008).

Studying dual-task performance has indicated the level of neural involvement in postural control and/or gait depends on the task constraints in the dual-task scenario (Li, Krampe et al. 2005, Yogev-Seligmann, Hausdorff et al. 2008). In the case of gait, walking performance while also completing the secondary task is compared to walking performance on its own. If a change in performance is noted for either the walking task (e.g. in walking speed, step length etc.) or cognitive performance (i.e. accuracy, response time etc.), it can be hypothesized that overlap exists in the cognitive resources to complete both tasks (See Figure 2.2). For this hypothesis to be meaningful, we must have an indication of the brain activity required to complete the cognitive task itself.

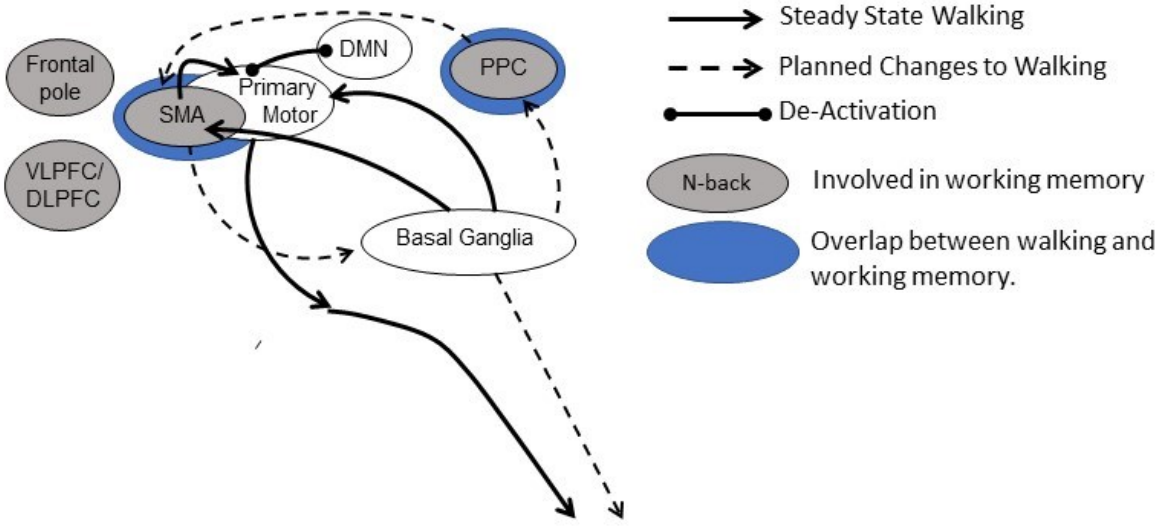

Figure 2.2: *Potential overlap between walking and the N-back task. Dual task methodology assesses cognitive control of walking by observing changes in walking performance while performing a secondary task. If a change in performance occurs, it is hypothesized that an overlap*

exists in cortical input between tasks. VLPFC: ventrolateral pre-frontal cortex; DLPFC: dorsolateral pre-frontal cortex; SMA: supplementary motor area; PPC: posterior parietal cortex; DMN: default mode network.

Higher order cognitive functions, such as executive functions are commonly used during dual-task paradigms. Executive functions are required for tasks such as response scheduling, allocation, inhibition or monitoring; goal-directed actions; maintaining, updating and executing abstract task plans; and processing and storing of visuo-spatial or verbal information (Yogev-Seligmann, Hausdorff et al. 2008). For instance, every day we take advantage of our ability to remember information, such as a new telephone number, for a brief time, and maintain and periodically refresh this information to respond a later time when it is time to dial the phone. This capability, known as working memory, encompasses a limited capacity temporary storage system under attentional control through a central executive able to manipulate and manage the information (Gevins and Cutillo 1993, Goldman-Rakic, Cools et al. 1996, Ravizza, Delgado et al. 2004, Baddeley 2007). Key to the differentiation of working memory from other types of memory is its temporary nature and its use in both cognitive and behavior tasks requiring integration of temporally separate information after a short latency (Fuster 1995).

N-Back Task

To explore the higher order cognitive requirements of walking on a split belt treadmill, the *n*-back task was employed (see Chapter 4). The *n*-back task is a widely used tool for studying working memory as it requires active maintenance of multiple stimuli in immediate memory and adjustment of behavior in response to feedback (Cohen, Forman et al. 1994, d'Esposito, Aguirre et al. 1998). In the most typical arrangement, the *2-back* task, participants must maintain two

previous stimuli in memory and judge whether the current cue matches the stimuli from 2 previous in the sequence (Gevins and Cutillo 1993, Baddeley 2007). The *n*-back task is cognitively demanding, as information must be continually adjusted and held in working memory, while incorporating the most recently presented stimuli and rejecting or ignoring more temporally distant stimuli (Owen 1997, Owen, McMillan et al. 2005). The continuous nature of the *n*-back task requires constant reshuffling of the contents held in working memory since different stimuli are simultaneously being stored, inhibited or recognized based on the stored representation of the cue and dropped from memory (d'Esposito, Aguirre et al. 1998, Smith and Jonides 1998). One of the best attributes of the *n*-back task is the ability to alter working memory load incrementally using a *0*-, *1*-, *2*- or *3*- back task, altering the temporal distance between cue and response (Braver, Cohen et al. 1997).

Neural Correlates of Working Memory

In order to make meaningful hypotheses of the supraspinal control of walking using dual task methodologies, we must first have a good understanding of the neural correlates of the secondary cognitive task used. There is no argument that the prefrontal cortex is central to carrying out higher order cognitive functions such as working memory (Yogev-Seligmann, Hausdorff et al. 2008, Al-Yahya, Dawes et al. 2011). Different executive functions activate or involve three distinct bilateral anatomical areas: the frontal pole (rostral PFC, Broadman Area (BA) 10), the dorsolateral (DLPFC, BA 9, 46) and the mid-ventrolateral PFC (VLPFC, BA 45, 47). The VLPFC is the first level of interaction of working memory with the posterior association areas and is the location of information organization and interaction between short-term and long-term memory systems and executive processing (Owen, Evans et al. 1996, d'Esposito, Aguirre et al. 1998, Owen 2000, Owen, McMillan et al. 2005). It is in this area that active comparisons and judgements of stored

information held in working memory are made (Petrides 1994, Petrides 1995, Owen, Evans et al. 1996, d'Esposito, Aguirre et al. 1998, Owen 2000). Both spatial and non-spatial stimuli are held 'online' and retrieval cues required to recognize stimuli are mapped and implemented to learned responses (Courtney, Ungerleider et al. 1997, Owen 2000, Dobbins, Foley et al. 2002). These comparisons and recognitions are central to the ability to respond to a cue with information held in working memory. The VLPFC is involved in management of task switching (Dove, Pollmann et al. 2000) and in reversal learning, the adaptation of behaviour according to a set of rules and rewards (Cools, Clark et al. 2002), which are both important for holding the requirements and rules of a working memory task 'on-line'.

The frontal pole, along with the DLPFC, has been implicated in the manipulation and evaluation of self-generated information including relational integration, known as the simultaneous consideration of multiple objects and their relation to each other (Düzel, Cabeza et al. 1999, Christoff, Prabhakaran et al. 2001, Kroger, Sabb et al. 2002). This area is also highly involved in retrieving contextual information, temporal organization of the experience, and hypothesis generation and evaluation of a self-generated response (Cabeza, Mangels et al. 1997, Düzel, Cabeza et al. 1999, Lepage, Ghaffar et al. 2000). Termed self-referential evaluation, this allows participants to generate a response in the context of stored information about the stimuli (Ravizza, Delgado et al. 2004). The frontal pole is also responsible for the process of branching, integrating working memory with attentional resource allocation. This aids in keeping a main goal in mind (i.e. responding to a correct cue) while performing other sub-goals (i.e. altering the current cue held in memory), and being able to return to the task at hand (Koechlin, Basso et al. 1999). This is of special importance for tasks involving more than one discrete cognitive process, tasks requiring coordination of information processing and transfer between multiple operations

(Ramnani and Owen 2004). Finally, the frontal pole becomes important to the process of prospective memory and carrying out delayed intentions, such as the delayed response during a working memory task (Burgess, Quayle et al. 2001).

The DLPFC is central to higher order executive processes as the area directed at active monitoring, the ability to 'check' online information, and manipulation of information within working memory (Petrides 1995, Owen, Evans et al. 1996, d'Esposito, Aguirre et al. 1998, Owen 2000, Ravizza, Delgado et al. 2004). This area is also responsible for active decisions about the occurrence or non occurrence of stimuli (Owen, Evans et al. 1996). The DLPFC organizes working memory contents into higher-levels and provides the strategic control of working memory information processing. Lesions within this area of the frontal lobe show an inefficient use of response organization strategies leading to inaccurate performance of a working memory task (Owen, Morris et al. 1996).

In addition to the PFC, the posterior parietal cortex (PPC) has been shown to be involved in the short-term storage requirements used for decision making during a working memory task (Smith and Jonides 1998). Dorsal inferior PPC activation is affected by cognitive load increases and serves to focus attention on items within working memory and is part of incorporating information within the frontal parietal executive system. Whereas the ventral inferior PPC is responsible verbal and non verbal information distinctions, for encoding verbal information and phonological short-term storage (Ravizza, Delgado et al. 2004).

Finally, while it has been assumed that activation of pre-motor cortex (PMC, BA 6,8) and supplementary motor areas (SMA, BA 6,32) is due to preparation by the PFC for movements or verbal responses during working memory tasks (d'Esposito, Aguirre et al. 1998), activations more specific to higher level cognitive functions have also been noted. The PMC and SMA are involved

in visuospatial attention maintenance during the delay between stimulus and response (Jonides, Smith et al. 1993, Owen, McMillan et al. 2005) and the articulatory rehearsal process (Smith and Jonides 1998, Ravizza, Delgado et al. 2004) required during working memory tasks.

Not surprisingly, working memory tasks highlight the use of multiple cortical areas for short-term storage, decision making based on stimuli recognition, response activation or inhibition and constant information refreshing and updating. Given the extensive use of the cortex to carry out a working memory task properly, completing this task simultaneous to walking would be an interesting intervention to assess the effect of increasing cognitive load on dual-task performance. An auditory version of the n-back task is employed in Chapter 4 to provide insight into the cognitive requirements of split belt treadmill walking in healthy young adults.

2.5 Assessing supraspinal control of walking: Positron Emission Tomography (PET) Imaging

Neuroimaging in humans, such as functional magnetic resonance imaging, has highlighted the existence of specific brain regions that regulate gait parameters (e.g. initiation/termination, obstacle navigation) during imagined locomotor tasks. The physical constraints of this imaging technique require participants to be lying down throughout the assessment, and as such are limited to small movements of the feet (i.e. plantar/dorsiflexion on foot pedals)(Mehta, Verber et al. 2009), watching videos or photos of others walking (Gilat, Shine et al. 2015), or imagining themselves walking in different environments (Jahn, Deutschländer et al. 2004, Jahn, Deutschländer et al. 2008). Of course, imagined and real locomotion are not the same. For example, upright body position, limb movements and sensory feedback do not exist during these imagined motor tasks.

Using ^{18}fluorine-fluorodeoxy-glucose Positron Emission Tomography (^{18}F-FDG PET) imaging, laFougere and colleagues (2010) were able to demonstrate whole brain activation during a motor task, providing insight into the specific brain regions active during real locomotion.

PET Imaging

Radioisotopes, unstable molecules with an excess number of protons, are used in PET imaging to map markers for physiological processes. Through β^+ radioactive decay, an excess proton transforms into a neutron, releasing a neutrino and a positron (i.e. an electron with a positive charge). Based on the positron's energy, it will travel a certain distance away from the molecule (2-3mm) until it reaches an electron. An annihilation of both molecules will then take place releasing two photons. The PET scanner is made up of pairs of photon detectors arranged in a ring around the patient, which absorb the photon energy and record the location of the annihilation incident. From these incidences, a map of annihilation locations is reconstructed, indicating where the radioactive tracer has accumulated.

^{18}F-FDG is a radioactive analog of glucose and is absorbed by the body's cells in the same manner. The rate of energy production from glucose through glycolysis is dependent upon the phosphorylation of glucose via hexokinase. Thus, the rate at which glucose is phosphorylated provides a measure of metabolism. In the tracer, ^{18}F-FDG, ^{18}F replaces two hydroxyl groups of normal glucose and once phosphorylated within the first step of glycolysis, is prevented from continuing in the glycolytic pathway, causing areas with increased metabolism to accumulate ^{18}F. By means of the progressive accumulation of a radioactive glucose analog to map whole brain metabolism, neural activity imaged with ^{18}F-FDG PET represents the brain's average activity over a 30 to 40-minute period. While this excludes ^{18}FDG PET for assessing events that take place over a short period, it does allow for the assessment of activities sustained over the entire uptake period,

such as walking. Previous ^{18}F-FDG PET protocols have successfully generated hypothesizes of the brain areas involved when modulation of the gait pattern is required (la Fougere, Zwergal et al. 2010, Mitchell, Potvin-Desrochers et al. 2018, Mitchell, Starrs et al. 2018). A similar protocol using ^{18}F-FDG PET imaging is employed in Chapter 5 and 6 to investigate the neural control of split belt treadmill walking in young healthy adults, healthy older adults and adults with Parkinson's disease.

2.6 Assessing Supraspinal Control of Walking: Changes due to Parkinson's Disease

In human research, clinical populations who have experienced a brain lesion due to disease or acute injury can provide a model for how the brain acts and controls walking with altered, diminished or non-existent input from one region. Parkinson's disease (PD) is a pathology of the basal ganglia, where the typical inhibitory pathways of the basal ganglia are over excited leading to a reduction of the excitatory signals sent via the thalamus to the cortex (Alexander, Crutcher et al. 1990, Buhmann, Glauche et al. 2003). This causes a reduced ability to produce smooth, coordinated movements, especially during sequential (Benecke, Rothwell et al. 1987) or complex movement control (Berardelli, Dick et al. 1986). Accordingly, adults with PD report a lack of control over limb movement, and a feeling as if they must "think" about each movement. One of the key symptoms of reduced movement control occurs during walking, where disease progression manifests as slower, shuffling gait (Morris, Iansek et al. 1994). However, despite these disease-related changes to automaticity of locomotor control, adults with PD can adapt their gait pattern to a split belt treadmill. Across a variety of paradigms, adults with PD adapt gait similarly to age-matched controls both in terms of gait variability and gait coordination (Seuthe, D'Cruz et al. 2019) and in both the ON and OFF Dopamine medication states (Nanhoe-Mahabier, Snijders et al. 2013,

Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Mohammadi, Bruijn et al. 2015). However, at later stages of PD, whereby participants experience freezing of gait, gait adaptation and perception of the belt speed discrepancy become more difficult (Nanhoe-Mahabier, Snijders et al. 2013, Mohammadi, Bruijn et al. 2015, Bekkers, Hoogkamer et al. 2017). Given the lack of difference between healthy older adults and adults with PD in altering their gait pattern to accommodate belts at different speeds, the role of the basal ganglia in altering the gait cycle could be questioned.

Alterations to activation of basal ganglia and cerebellum are both a result of PD. Both the basal ganglia and cerebellum are activated for new learning of a movement, activation that is not simply due to the action being carried out (Jueptner, Frith et al. 1997, Jueptner, Stephan et al. 1997). The basal ganglia project to multiple cortical areas via the thalamus, many of which would be active during locomotion: primary motor, premotor, and SMA, pre supplementary motor area, and cingulate. In addition, there is evidence of compensatory changes in cortical activation during movement in adults with PD that is not limited to diminished activation of the basal ganglia. For instance, joystick movements at rest saw impaired activation of putamen, anterior cingulate, SMA and DLPFC (Playford, Jenkins et al. 1992). Even in early stage PD, when motor impairments may be minimal and/or only unilateral, still see decreased activation in bilateral SMA and contralateral primary motor area to hand movements that is reversed back to normal with dopamine medication (Buhmann, Glauche et al. 2003). During continuous steering of the walking pattern, adults with PD increased activity of the PPC and decreased activity in the DLPFC compared to typical straight walking with further changes occurring with disease severity (Mitchell, Potvin-Desrochers et al. 2019). However, the variety of cortical and subcortical studies of PD do not fully explain how adults with PD can walk on the split belt treadmill without further deficits to their gait pattern. By

comparing gait biomechanics and brain activity between adults with and without PD, we can better understand the role of the basal ganglia in the gait adjustment and adaptation process.

2.7 Conclusion

Ongoing adjustments to the gait pattern and gait adaptation are crucial to moving through our environment without falling or causing injury. The human CNS is capable of not only maintaining a symmetrical walking pattern with an externally applied unilateral perturbation but also storage of the appropriate pattern to respond. Based on our understanding of the neural control of planned changes to the walking pattern, it is clear that higher order cognitive functions from the motor and sensory cortices along with the cerebellum are key to anticipatory gait changes and storage of an adapted gait pattern. Short-term storage, evidenced by post-adaptation aftereffects, and longer-term retention, demonstrated by a quicker rate of adaptation on a second bout, illustrate the capabilities for neurorehabilitation of a secondary gait pattern. Consequently, the work of this doctorate will provide important background for further discussion and research to understand how a brain recovering from injury or disease may function differently in gait adaptation. To better understand the current body of literature and its hypotheses related to the neural control of split belt treadmill adaptation, a systematic review of the literature was carried out (Chapter 3). While a few descriptive reviews of split belt literature do exist, they are limited to a smaller portion of the existing literature or focused on a single pathology (Reisman, Bastian et al. 2010, Torres-Oviedo, Vasudevan et al. 2011, Helm and Reisman 2015, Seuthe, D'Cruz et al. 2019). A full systematic review of the current split belt treadmill literature has not yet been published to consolidate what is known about how the human CNS is able to adapt to this type of symmetry perturbation. This type of review allowed for a wide variety of different split belt paradigms to be

summarized and their hypotheses compared. This first thesis study provides a model of the neural control of adaptation based on all existing literature from a variety of human populations.

Chapter 3: Understanding human neural control of gait adaptation to the split belt treadmill: A systematic review

THESIS STUDY 1

Authors: Dorelle C. Hinton[1,2], David Conradsson[1,3,4], Caroline Paquette[1,2*]

Affiliations:

[1] Department of Kinesiology & Physical Education, McGill University, Canada

[2] Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR)

[3] Department of Neurobiology, Health Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Sweden

[4] Function Area Occupational Therapy & Physiotherapy, Allied Health Professionals Function, Karolinska University Hospital, Stockholm, Sweden

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3.1 Abstract

A full systematic review of the current split belt treadmill literature has not yet been published to consolidate what is known about how the human CNS controls adaptation to this type of symmetry perturbation. A systematic literature search identified 61 studies that investigated the neural control of human gait adaptation to a split belt treadmill. Studies of infants and manipulated sensory feedback in healthy adults suggest that the initial gait adjustments to split belt walking is reliant on proprioceptive feedback to inform central pattern generators to modify lower limb muscle activation patterns appropriately. Simultaneously, this literature suggested that proprioceptive and visual feedback inform supraspinal centres for motor planning and motor output to adapt and store a new and efficient gait pattern to walk on belts at different speeds. However, evidence from participants with brain injury (post-stroke, cerebellar lesions) suggest that injury impedes, but does not completely take away, the ability to adjust and adapt aspects of the gait pattern to split belts.

Highlights:

- We reviewed studies of human gait adaptation to the split belt treadmill.
- We propose a model describing the roles of the human CNS during gait adaptation.
- Initial adjustments to split belts rely on proprioceptive feedback to spinal circuits.
- Adaptation requires cognitive and cerebellar influence to learn a new gait pattern.
- However, despite altered neural control, clinical populations can adapt the gait pattern.

Keywords: split belt treadmill, gait adaptation, neural control

3.2 Introduction

On a daily basis, we adjust our symmetrical walking pattern for walking straight ahead, to an asymmetrical pattern using different step lengths to steer the body in a new direction or navigate a crowded street. In the laboratory, this ability to adjust and adapt the walking pattern has been studied using a split belt treadmill, where each leg is driven independently with two belts driven at different speeds. Early split belt treadmill work was focused on whether the human locomotor plan could adjust to the asymmetrical requirements of split belt treadmill walking and observed the required changes to the kinematics, kinetics, and muscle activation patterns for healthy infants and young adults to walk on belts at different speeds (Thelen, Ulrich et al. 1987, Dietz, Zijlstra et al. 1994, Dietz, Zijlstra et al. 1995, Prokop, Berger et al. 1995, Zijlstra and Dietz 1995). From the earliest work, it became clear that infants and adults can adjust the gait cycle to walk on split belts within 20 strides of exposure (Thelen, Ulrich et al. 1987, Prokop, Berger et al. 1995, Zijlstra and Dietz 1995).

In order to walk on belts driven at different speeds, immediate adjustments of the gait cycle create a characteristic limping mimicking the asymmetry presented by the speed difference between belts. First, to accommodate an increase in time spent in double support and maintain a 1:1 stepping ratio, the gait cycle time is lengthened (Zijlstra and Dietz 1995, Reisman, Block et al. 2005). At the same time, the leg driven by the slower belt, known as the “slow” leg, increases time spent in stance while the leg driven by the faster belt, known as the “fast” leg, increases time spent in swing (Dietz, Zijlstra et al. 1994, Prokop, Berger et al. 1995, Zijlstra and Dietz 1995, Reisman, Block et al. 2005). The changes in each leg (i.e. on slow and fast belts) affects the strength and timing of the muscle activation in the other, and thus proprioceptive feedback from each leg is

being used to calibrate the amount of swing and stance required (Dietz, Zijlstra et al. 1994, Prokop, Berger et al. 1995).

Gait adaptation to the split belt treadmill

By assessing how the human walking pattern adapts over the course of a 10 to 15-minute exposure to split belts, Reisman and colleagues (2005) demonstrated the presence of motor adaptation on the split belt treadmill. From this extended exposure, they were able to demonstrate that gait pattern changes were not simple adjustments of the gait cycle to the different belt speeds but also entailed more complex processes since aftereffects, in the form of a limp upon returning to typical treadmill walking, were present (Reisman, Block et al. 2005). Evidence from this body of work points to the human central nervous system (CNS) working towards both biomechanical and metabolic efficiency as participants alter the asymmetric gait cycle to be smoother, more symmetric gait pattern throughout adaptation. For instance, braking, propulsive, and medio-lateral ground reaction forces have shown to decrease over the course of adaptation to similar levels of typical steady-state gait (Ogawa, Kawashima et al. 2012, Mawase, Haizler et al. 2013, Ogawa, Kawashima et al. 2014, Ogawa, Obata et al. 2018). Lower limb muscle activity also adapts from chaotic activity to characteristic bursts of typical gait (Dietz, Zijlstra et al. 1994). Temporal shifting of the gait pattern relative to toe-off (Maclellan, Ivanenko et al. 2014) has informed the hypothesis that the heel contact of each step is used in feedforward manner to predict the optimal placement of the next step (Mawase, Haizler et al. 2013). Since interlimb aspects of the gait cycle (phasing, step length) change slowly over adaptation (Reisman, Block et al. 2005, Malone and Bastian 2010, Malone, Bastian et al. 2012), step length symmetry and dual-support symmetry are frequent kinematic metrics to investigate split belt treadmill adaptation. Finally, it has been observed that over the course of adaptation, the reduction in step asymmetry is associated with an improved

metabolic efficiency (Finley, Bastian et al. 2013). This adaptation paradigm became the go-to setup for most future human split belt treadmill work.

Hypotheses of central nervous system control of gait adaptation

Through the extensive study of healthy, young participants, it became clear that a broad network of the CNS is required for split belt adaptation to occur. The primary hypothesized region for adaptation has been the cerebellum as a site for feedback-driven updates to the locomotor plan (Bastian 2006, Malone and Bastian 2010, Malone, Bastian et al. 2012). Increased activity from cerebellar climbing fibers during locomotion provide feedback to the cerebrum on error detected during stance phase in preparation for the swing phase of the next step (Yanagihara and Udo 1994). The fact that the cerebellum is a key integration site for motor and sensory feedback also bolsters the suggestion that proprioceptive feedback is a requirement for adaptation to be possible. The posterior parietal cortex (PPC) is hypothesized to integrate limb movements and environmental information to create and update a body schema (Takakusaki 2013). Using imaging of brain metabolism, the PPC demonstrated increased activity during complex turning tasks while walking and continuous adjustments of the gait pattern to treadmill belt speeds (Mitchell, Starrs et al. 2018, Hinton, Thiel et al. 2019, Mitchell, Potvin-Desrochers et al. 2019). Together with the anterior cingulate cortex and supplementary motor areas, these cortical regions are hypothesized to play a role in visuo-motor integration and error monitoring (Gwin, Gramann et al. 2011, Hinton, Thiel et al. 2019), and are therefore regions that likely play a key role in gait adaptation. Finally, the basal ganglia is responsible for integrating volitional and automatic processes of the cortical control of posture and movement (Takakusaki, Saitoh et al. 2004) and along with premotor cortical areas is hypothesized to be involved in modulation of the walking plan (la Fougere, Zwergal et al. 2010).

Studying the neural control of split belt adaptation

Participants with altered input from the cerebellum (i.e. cerebellar degeneration or lesion), the cerebrum (i.e. post stroke, traumatic brain injury (TBI), cerebral palsy), or the basal ganglia (i.e. Parkinson's disease) provide insight into the relative role of these areas for the split belt adaptation process. In addition, amplifying or dampening activity in specific brain areas of healthy participants using non-invasive brain stimulation (i.e. paired coil transcranial magnetic stimulation [TMS] or transcranial direct current stimulation [tDCS]) has been used to understand the contribution of these regions for split belt adaptation. Less invasive changes to cerebral activity can be induced using a dual-task paradigm, where participants are asked to attend to and complete a simultaneous cognitive task while walking. The change in performance from walking alone and walking and completing a cognitive task provides insight into the potential cerebral overlap between higher-order cognitive areas and brain areas required for walking (Yogev-Seligmann, Hausdorff et al. 2008). Finally, studies involving healthy participants using paradigms that altered sensory feedback (i.e. plantar vibration, altered optic flow, altered body weight) or immature CNS (i.e. infants, toddlers) provide insight into the requirements from either the sensory feedback systems or influence of central pattern generators into the split belt adaptation process.

While a few descriptive reviews of split belt literature do exist, they are limited to a smaller portion of the existing literature or focused on a single pathology (Reisman, Bastian et al. 2010, Torres-Oviedo, Vasudevan et al. 2011, Helm and Reisman 2015, Seuthe, D'Cruz et al. 2019). A full systematic review of the current split belt treadmill literature has not yet been published to consolidate what is known about how the human CNS is able to adapt to this type of symmetry perturbation. This review set out to provide an up-to-date and current consolidation of the major hypotheses for the neural control of human gait adaptation to the split belt treadmill. It aimed to

systematically review the literature to consolidate the key hypotheses to date for the role(s) of the CNS in the initial gait adjustments and in completing a full adaptation of the motor system to the symmetry perturbation induced by a split belt treadmill.

3.3 Methods

Search Strategy

A systematic literature search was carried out in *PubMed*, *OVID MedLine*, and *Web of Science* databases of papers published or in press up until May 31, 2019 (Prospero ID: 148329). Search strategy keywords were selected based on common terms used in the split belt treadmill literature: (Walk* OR Gait OR Locomot*) AND (Treadmill OR adapt* OR coordination OR asymmetry* OR symmetry* OR learn*) AND Split belt. Search key words were entered as "All Fields" (*PubMed*), "Keyword" (*Ovid Medline*) or "Topic" (*Web of Science*). All identified published articles were exported to Rayyan (Ouzzani, Hammady et al. 2016) and Endnote X9 (Thomas Reuters, NY) for screening (Figure 3.1).

Study Selection

Once duplicate studies were removed, study titles and abstracts were screened (n=311). Only studies in English, which investigated the neural control of split belt treadmill walking in humans were included. Studies had to include participants with a clinical condition affecting the CNS, healthy participants who experienced a specific study intervention relating to the neural control of locomotion during split belt treadmill walking or infants or toddler prior to independent and mature walking patterns. Excluded studies included participants with clinical conditions or injuries outside of the CNS (e.g. amputee, anterior cruciate ligament reconstruction), or

interventions with healthy participants that focused on the biomechanics of gait adaptation (e.g. exoskeletons, different types of belt speed changes). Animal experiments were excluded.

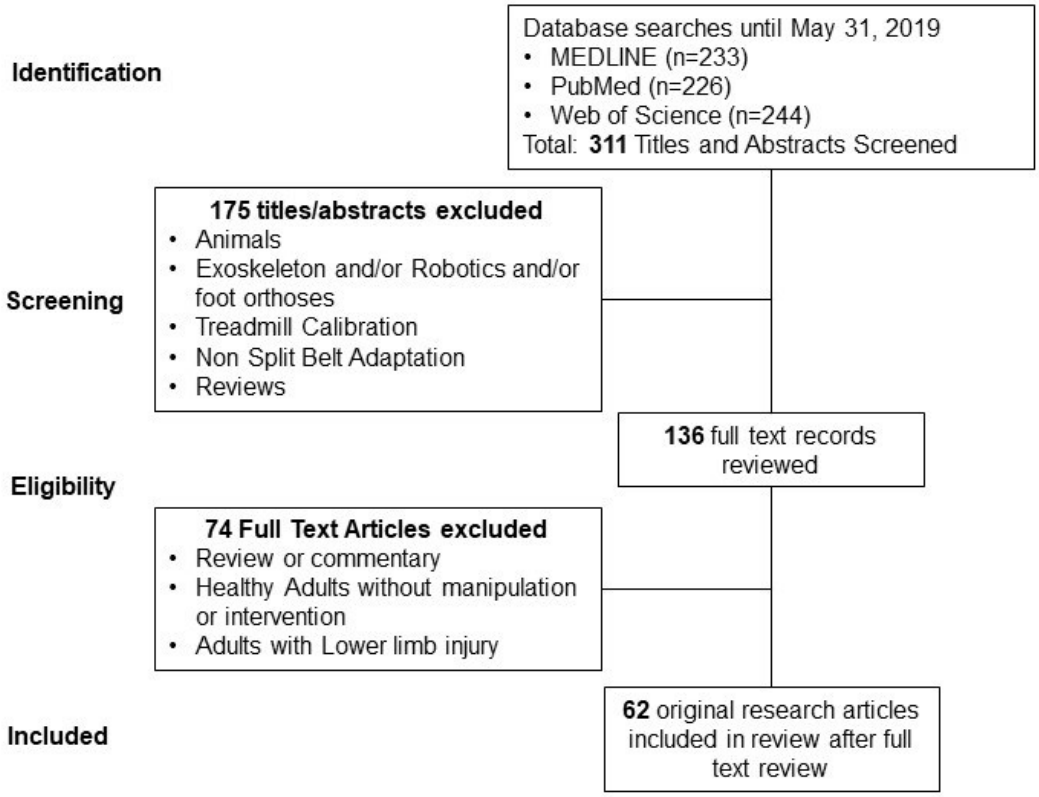

Figure 3.1: *Process of study selection. Once database searches were complete and duplicates were removed, study titles and abstracts and then full texts were screened to ensure they were investigating the human central nervous system's control of gait adaptation to the split belt treadmill.*

Data Extraction

Once initial screening of study titles and abstracts was completed, the entirety of included studies was analyzed (n=62). Descriptive information from each study regarding study design, subject characteristics (age, sex, pathology) and split belt methodology were summarized. Studies

were then grouped in five categories based on the overlapping theme of their research question(s) and findings:

1. **Role of Cerebellum:** Studies assessed potential cerebellar involvement in split belt treadmill adaptation through participants who have altered cerebellar activation either due to cerebellar degeneration, lesion or external stimulation via TMS or tDCS (Table 3.1). To gather information of cerebellar influence, these studies either compared participants with cerebellar lesion to healthy age-matched controls, compared two groups of healthy young adults (tDCS vs control), or measuring cortical excitability via TMS pre and post split belt adaptations.
2. **Role of Cerebrum:** Cerebral involvement in split belt treadmill adaptation was evaluated through participants with cortical and subcortical pathology due to lesions post-stroke, cerebral palsy, post-hemispherectomy or TBI or altered requirements from the cortex due to a simultaneous dual task (Table 3.2). To better understand of cerebral control, these studies either compared performance of participants post-stroke, TBI, cerebral palsy or post-hemispherectomy to healthy age-matched controls or compared split belt adaptation in healthy adults with and without a secondary task requiring cognitive input.
3. **Role of Basal Ganglia:** Basal ganglia involvement in split belt treadmill adaptation was observed in participants who have altered use of the basal ganglia due to Parkinson's disease or focal dystonia (Table 3.3). To investigate the role of the basal ganglia, these studies compared performance of participants in PD or focal dystonia to healthy age-matched controls.
4. **Role of Central Pattern Generators (CPG's):** The potential involvement of central pattern generators in split belt adaptation was investigated through infant and toddler

participants without independent of fully matured locomotor skills (Table 3.4). To better understand the potential role of CPG's, these studies observed infants or compared infants to toddlers at various points in development of mature walking control.

5. **Role of Sensory Feedback:** The role of sensory feedback during split belt adaptation was assessed using paradigms that altered body weight, visual, optic flow or movement feedback, vestibular or muscle stimulation, or with plantar vibration (Table 3.5). Sensory feedback manipulations in healthy adults allowed for observations and hypotheses to be made on the role of different types of sensory feedback.

3.4 Results

Study Selection and Characteristics

The literature search yielded a total of 703 results (Figure 3.1). Once duplicates were removed, 311 titles/abstracts and then 136 full texts were screened for inclusion and exclusion criteria. We identified 62 studies that investigated humans walking on a split belt treadmill who were affected by a clinical condition affecting the CNS, healthy participants with an intervention affecting the CNS' control of walking (e.g. brain stimulation, dual tasking, altered visual feedback), or infants and toddlers prior to independent or mature walking patterns. Of the 62 studies included in the review, 6 studies investigated the role of cerebellum (Table 3.1), 31 studies investigated the role of cerebrum (Table 3.2), 8 studies investigated the role of basal ganglia (Table 3.3), 3 studies investigated the role of CPGs (Table 3.4) and 14 studies investigated the role of sensory feedback (Table 3.5) in locomotor adaptation to the split belt treadmill.

Role of Cerebellum

Initial adjustments to the split belt paradigm in participants with cerebellar lesion(s) remain quick and mostly unaltered from healthy participants, as shown in Figure 3.2 (Morton and Bastian 2006, Hoogkamer, Bruijn et al. 2015). During adaptation, two studies observed differences in belt speed perception in adults with cerebellar lesion(s) compared to healthy controls (Hoogkamer, Bruijn et al. 2015, Statton, Vazquez et al. 2018). In the early stages of adaptation, perception of belt speeds was correlated to stance time in the slow leg (Hoogkamer, Bruijn et al. 2015). Adults with cerebellar lesions were able to adapt step length symmetry but were unable to perceive differences in each leg's steps post adaptation (Statton, Vazquez et al. 2018). Stimulation of cerebellum throughout adaptation via anode stimulation with transcranial direct stimulation (tDCS) increased the rate of adaptation of spatial aspects of the gait cycle, but not temporal (Jayaram, Tang et al. 2012). In contrast, inhibition of the cerebellum throughout adaptation via cathode stimulation with tDCS slowed adaptation (Jayaram, Tang et al. 2012). The overall split belt adaptation process caused an increase in cerebellar excitability, with the magnitude of change related to participants' degree of adaptation (Jayaram, Galea et al. 2011). Overall, adaptation caused a reduction in the cerebellum's normal inhibitory tone over the primary motor area beyond typical walking (Jayaram, Galea et al. 2011).

Two studies observed that cerebellar lesions lead to smaller aftereffects post-adaptation (i.e. impaired storage of the new gait pattern) compared to healthy participants and that aftereffects were associated with the severity of motor impairments (Morton and Bastian 2006, Hoogkamer, Bruijn et al. 2015). Participants with cerebellar lesions with the least motor impairment showed the largest aftereffects, indicating better storage of the new gait pattern than those with more severe motor impairment (Morton and Bastian 2006). Cerebellar stimulation during adaptation with tDCS

(anode or cathode) did not affect aftereffects or the post-adaptation phase compared to sham stimulation (Jayaram, Tang et al. 2012).

Table 3.1: Investigating the role of the cerebellum in split belt adaptation.
All studies used a variation of the adaptation protocol including an extended exposure to split belts. *SB: split belt; TB: tied-belt; AE: aftereffects; SLS: step length symmetry; DSS: dual support symmetry; TMS: transcranial magnetic stimulation; M1: primary motor area; tDCS: transcranial direct stimulation*

Author (Year)	Participants	Mean Age±SD	Location of lesion/stimulation	Main Findings
Cerebellar Lesion				
1. Morton & Bastian (2006)	9 cerebellar degeneration; 17 healthy	46.3±8.6	Diffuse cerebellar degeneration; Nonspecific localization.	Feedback-driven outcomes altered quickly in both SB and TB; Small AE in cerebellar lesion patients
2. Hoogkamer et al. (2015)a	8 cerebellar lesion post tumour resection; 9 healthy;	20.6±3.6; 25.9±5.2	Majority in vermis, bilateral paravermis and unilateral hemisphere.	Perception of belt speeds correlated to stance time of slow leg; Deficits were mild despite cerebellar lesions; Spatial asymmetry is maintained, rather than corrected, whereas temporal asymmetry is corrected if participants can perceive differences.,
3. Hoogkamer et al. (2015)b	15 cerebellar lesion cerebellar lesion post tumour resection; 13 healthy	23±6.2; 25.3±4.6	Majority in vermis, bilateral paravermis and unilateral hemisphere.	No difference from healthy controls for interlimb measures (SLS, DSS). Even those mildly affected by cerebellar lesion showed gait changes during SB adaptation. Participants with greatest baseline gait asymmetry had lesions in vermal lobules VI and crus II.
4. Statton et al. (2018)	8 cerebellar damage; 8 healthy	32- 69, 32-72	Diffuse cerebellar damage, nonspecific localization; cerebellar ataxia, cerebellar stroke	Some of early adaptation can be perception driven- severity of ataxia affects the ability to perceive these differences
Healthy with excitatory dual coil TMS: Cerebellum and Motor Cortex				
5. Jayaram et al. (2011)	9 Healthy	19-25	TMS measures completed before and after split belt adaptation. Conditioning TMS pulse over cerebellar cortex ipsilateral to dominant leg (3 cm lateral to inion on line joining inion and the external auditory meatus) was delivered 5 ms prior to testing stimulus over contralateral M1	Cerebellar excitability increased after SB adaptation, and its change in magnitude was related to participants' degree of adaptation; SB adaptation reduced normal inhibitory tone the cerebellum exerts over M1.
Healthy with tDCS				
6. Jayaram et al. (2012)	Experiment 1: 40 Healthy; Control 1: 8 Healthy; Control 2: 5 Healthy	20 -33; 22-31; 23-30;	tDCS stimulation (anodal, cathodal or sham) over the cerebellum (3 cm lateral to the inion) during entire adaptation period. Groups separated by anode, cathode or sham placed over ipsilateral to fast leg.	Anodal stimulation of fast leg increased rate of adaptation while cathodal slowed adaptation. No change to AE. Anodal stimulation increases cerebellar cortex engagement.

Role of Cerebrum

Unspecific cerebral lesions stemming from stroke, CP or TBI as well as research paradigm involving a dual-task led to rapid initial gait adjustments accommodating speed changes but inducing larger perturbations to gait symmetry, despite the same magnitude of belt speed changes (Reisman, Block et al. 2005, Reisman, Wityk et al. 2007, McFadyen, Hegeman et al. 2009, Sawers, Kelly et al. 2013, Malone and Bastian 2014, Vasudevan, Glass et al. 2014, Mawase, Bar-Haim et al. 2016, Levin, Lewek et al. 2017, Vervoort, den Otter et al. 2019), especially to the leg on the slow belt (Mieville, Lauziere et al. 2018). Adults post-stroke are able to adjust the temporal aspects of the gait cycle to the split belts (i.e. stride time, swing time, limb excursion) with an increase in overall lower limb muscle activity (Malone and Bastian 2014). Two studies observed reduced cognitive performance in dual-task in the initial adjustment phase of split belt walking, (Sawers, Kelly et al. 2013, Vervoort, den Otter et al. 2019), especially with an abrupt change in belt speeds (Sawers, Kelly et al. 2013), suggesting an increase demand for frontal regions in the initial adjustment phase.

Despite a cortical or subcortical lesion affecting motor control of the lower limbs, participants post-stroke showed evidence of adaptation and de-adaptation of their gait cycle to the split belt treadmill(Reisman, Wityk et al. 2007, Reisman, Wityk et al. 2009, Malone and Bastian 2014, Helm, Tyrell et al. 2016, Lauziere, Mieville et al. 2016, Betschart, Lauziere et al. 2017, Alcantara, Charalambous et al. 2018, Cherry-Allen, Statton et al. 2018, Mieville, Lauziere et al. 2018, Helm, Pohlig et al. 2019). Adaptation of lower limb muscle activity in adults post-stroke was found to become more economical (Malone and Bastian 2014, Betschart, Lauziere et al. 2017) however, a weakness in plantar flexion may limit the capacity to reach step length symmetry (Lauziere, Mieville et al. 2016). Adaptation of spatial (i.e. foot placement relative to trunk position)

and temporal (i.e. step timing and trailing limb angular velocity) are independent in adults post-stroke, similar to healthy adults (Finley, Long et al. 2015). Two studies focused on the perturbation direction (which side slowed down) and size (speed difference between sides) (Tyrell, Helm et al. 2015, Wutzke, Faldowski et al. 2015) in participants with baseline gait asymmetry. It was found that the magnitude of split belt asymmetry must first exceed participant's baseline asymmetry (Wutzke, Faldowski et al. 2015), however, if the initial baseline asymmetry reduces baseline asymmetry, adults post-stroke will adapt more slowly and to a lesser extent than if the split belt asymmetry accentuates baseline step asymmetry (Tyrell, Helm et al. 2015). Over the course of adaptation, reaching step symmetry by participants post-stroke did not improve overall walking balance and the leg on the slow belt was always the most challenged (Mieville, Lauziere et al. 2018).

Contrary to most stroke lesions that were typically delineated lesions, participants with TBI, with more diffuse lesions, are also able to gradually adapt step length symmetry, but gait phasing did not completely adapt (Vasudevan, Glass et al. 2014). In participants completing a secondary cognitive task requiring a broad network of prefrontal cortical areas, two studies found that performance of a dual task slowed the rate of adaptation (Malone and Bastian 2010, Malone and Bastian 2016), specifically adaptation of spatial aspects of gait, but not temporal (Malone and Bastian 2010). Children post hemispherectomy, where one cortical hemisphere has been removed, were able to adapt spatial aspects of gait similar to typically developing children but not temporal aspects of walking (Choi, Vining et al. 2009).

Eight studies in adults post-stroke and two studies in adults with cerebral palsy found that repeated exposure to the adaptation protocol was effective in reducing the initial step-to-step asymmetry by augmenting the inherent symmetry present in participant's gait (Reisman, McLean

et al. 2010, Reisman, McLean et al. 2013, Tyrell, Helm et al. 2014, Mawase, Bar-Haim et al. 2016, Levin, Lewek et al. 2017, Betschart, McFadyen et al. 2018, Betschart, McFayden et al. 2018, Charalambous, Alcantara et al. 2018, Lewek, Braun et al. 2018, Helm, Pohlig et al. 2019). However, only targeted aspects of the gait cycle (i.e. symmetry) see this improvement with repeated bouts, and does not translate to other aspects of the gait cycle (Reisman, McLean et al. 2013).

Storage of the newly learned split belt pattern is not affected post-stroke (Tyrell, Helm et al. 2014, Lauziere, Mieville et al. 2016, Betschart, Lauziere et al. 2017, Alcantara, Charalambous et al. 2018, Betschart, McFayden et al. 2018, Charalambous, Alcantara et al. 2018, Cherry-Allen, Statton et al. 2018, Lewek, Braun et al. 2018, Helm, Pohlig et al. 2019). One study confirmed that the aftereffects present in the plantar flexor moment from midstance to initial swing contributed to the alteration of the contralateral step length in participants post-stroke (Lauziere, Mieville et al. 2014). While performance of a dual task was shown to affect adaptation, there was no evidence of it affecting the rate of de-adaptation or "forgetting" of the adapted gait pattern (Malone and Bastian 2010, Malone and Bastian 2016). Similar to typically developing children, children post hemispherectomy demonstrated savings of the newly learned gait pattern, especially for the spatial aspects of the gait cycle (Choi, Vining et al. 2009)

Table 3.2: Investigating the role of the cerebrum in split belt treadmill adaptation.
All studies used a variation of the adaptation protocol including an extended exposure to split belts unless specified with ** to indicate short bouts of split belt and tied-belt walking were compared. *OG: over ground; SB: split belt; AE: aftereffects; EMG: electromyography; SLS: step length symmetry; PF: plantar flexor*

Author (Year)	Participants	Mean Age±SD	Lesion Location / Impairment	Main Findings
Post Stroke				
7. Reisman et al. (2007)	13 post stroke, 13 healthy	27-70	Variety of locations, unilateral cortical or subcortical.	Post stroke able to rapidly accommodate speed changes, Post- stroke showed evidence of adaptation and post-adapt effects.
8. Reisman et al. (2009)	11 post stroke, 11 healthy	35 to 70	Variety of locations, unilateral cortical or subcortical.	Post- stroke showed evidence of adaptation and post-adapt effects; Transfer to OG walking possible - walking OG washed out learning on SB = same circuitry
9. Reisman et al. (2010)	Case Study Post stroke	36	Hemorrhagic stroke in right insular region.	Augmenting error improved training effects.
10. Reisman et al. (2013)	13 post stroke	36-70	Unilateral, no specified locations.	Only targeted aspects (symmetry) endure improvement with training, not invariant aspects; Augmenting error improved training effects
11. Lauziere et al (2014)	20 post stroke, 10 healthy	49.3±13.2; 57.6±17.2,	Location not specified, unilateral paresis.	Post stroke - AE present in plantar flexor moment from mid-stance to initial swing; Plantar flexor moment contributes to contralateral step length
12. Malone et al. (2014)	22 post stroke	24 to 87	Variety of locations, unilateral cortical or subcortical.	Temporal aspects of gait adjust to walk on SB: stride time, swing time, limb excursion, EMG greater in early adapt; Adaptation - EMG becomes more economical, maintained post-stroke
13. Tyrell et al. (2014)	16 post stroke, 16 healthy	62.75±8.24; 64.56±7.93	Variety of locations, unilateral cortical or subcortical.	Repeated exposure – post stroke able to reduce initial SLS – retention is not affected
14. Finley et al. (2015)	25 healthy, 15 post stroke	25±4; 58±14	Location not specified, unilateral paresis.	Spatial and temporal adaptation are separate and depend on different gait features in order to adapt (i.e. foot placement and step timing).
15. Tyrell et al. (2015)	17 post stroke	46 - 78	Location not specified, unilateral paresis.	Post-stroke adapted more slowly and to lesser extent when initial SB reduces step length asymmetry
16. Wutzke et al. (2015)	30 post stroke	58.6±13.4	Location not specified, no cerebellar or brain stem stroke.	SB asymmetry needs to exceed baseline asymmetry
17. Helm et al. (2016)	27 post stroke	BDNF polymorphism: 67.75±9.5; w/out: 67±6.7	Variety of locations, unilateral cortical or subcortical.	Post- stroke showed evidence of adaptation and post-adapt effects; BDNF polymorphism in stroke slowed rate of spatial adaptation
18. Lauziere et al (2016)	20 post stroke	49.4±13.2	Location not specified, unilateral stroke.	Post- stroke showed evidence of adaptation and post-adapt effects; PF weakness may limit capacity to increase SL
19. Betschart et al. (2017)	16 post stroke	49.8±13.4	Location not specified. Cerebral stroke only.	Post- stroke showed evidence of adaptation and post-adapt effects; Participants demonstrated the capacity to modify distal muscle activity in combination with step length

Author (Year)	Participants	Mean Age±SD	Lesion Location / Impairment	Main Findings
20. Alcantara et al. (2018)	26 post stroke	59±13	Location not specified, unilateral stroke.	Post-stroke showed evidence of adaptation and post-adapt effects. When asymmetry is presented abruptly, rather than gradually, participants have reduced transfer to OG.
21. Betschart et al. (2018)	12 post stroke	53.3±8.7	Location not specified, no cerebellar stroke.	Repeated exposure – post stroke able to reduce initial SLS – retention is not affected
22. Betschart et al (2018)	12 post stroke	53.3±8.7	Location not specified, unilateral stroke.	Repeated exposure – post stroke able to retain improvements in stride symmetry, augmenting error improved training effects.
23. Charalambous et al. (2018)	37 post stroke	Group 1:57±9; Group 2: 55±16; Group 3: 62±10	Location not specified, no cerebellar stroke.	Repeated exposure – post stroke able to reduce initial SLS – retention is not affected
24. Cherry-Allen et al. (2018)	12 post stroke	61±8	Location not specified, no cerebellar stroke.	Post- stroke showed evidence of adaptation and post-adapt effects
25. Lewek et al (2018)	47 post stroke	59±12	Location not specified, no cerebellar stroke.	Repeated exposure – post stroke able to reduce initial SLS – retention is not affected
26. Mieville et al (2018)	20 post stroke	49.4±13.2	Location not specified, no cerebellar stroke.	Post-stroke showed evidence of adaptation and post-adapt effects. Leg most challenged is the slow leg
27. Helm et al. (2019)	32 post stroke	59±11; 62±10	Variety of locations, cortical and subcortical, no cerebellar stroke.	Post- stroke showed evidence of adaptation and post-adapt effects; Repeated exposure – post stroke able to reduce initial SLS – retention is not affected
Post Traumatic Brain Injury (TBI)				
28. Vasudevan et al. (2014)	14 TBI, 11 healthy	29.7±9.3; 31.1±8.3	Moderate to severe, non penetrating TBI.	TBI – immediate change to stride length and stance time maintained but more perturbed by SB; TBI – able to gradually change SLS, centre of oscillation (phasing) did not completely adapt
Healthy with Cognitive Dual Task				
29. McFadyen et al. (2009)**	11 Healthy	26.2±3.8	-	Dual task did not affect stride timing or variability, increased dual support phase, asymmetric gait does require attention due to increased dynamic balance requirements
30. Malone et al. (2010)	33 Healthy	23.6	-	Dual task slows rate of adaptation for spatial aspects (not temporal)
31. Sawers et al. (2013)	20 Healthy	23-50	-	Gradual onset of belt asymmetry reduced effect of adaptation on dual task performance.
32. Malone et al. (2016)	10 Young, 20 Older	22.5±2.6; 54.9 ±2.8; 52.8±5.8	-	Dual Task slows down learning but does not remove participant's "forgetting" of newly learned gait pattern.
33. Hinton et al (2018)**	13 Healthy	23±3	-	Dual task did not affect stride timing or variability.

Author (Year)	Participants	Mean Age±SD	Lesion Location / Impairment	Main Findings
34. Vervoort et al (2019)	10 Young 12 Older	21.5±1, 68± 6	-	Dual task did not affect stride timing or variability. Reduced dual task performance early in adaptation.
Adults with Cerebral Palsy (CP)				
35. Mawase et al. (2016)	6 CP, 9 healthy	17.4±2.6; 19.4±0.5	Bilateral diplegia	Participants with CP demonstrated initial deficits in adaptation resulting in increased variability, but adaptation possible.
36. Levin et al. (2017)	5 CP	24-69	n=2 hemiplegic, n=3 diplegic	Adaptation possible, repeated bouts of split belt adaptation reduced gait asymmetry.
Children post hemispherectomy				
37. Choi et al. (2009)	10 post hemispherectomy, 10 healthy	7 to 18 y	Hemidecortication – unihemispheric cortical grey matter removed, white matter and ventricles left intact.	Children post hemispherectomy showed normal feedback adjustments; Children post hemispherectomy were able to adapt spatial aspects of gait similar to control but not temporal aspects of walking.

Role of Basal Ganglia

Participants with PD or focal dystonia can quickly adjust their gait cycle to the asymmetry of split belts (Dietz, Zijlstra et al. 1995, Hoffland, Veugen et al. 2014). However, participants with PD with freezing of gait were worse at perceiving difference between belts than those without freezing of gait (Bekkers, Hoogkamer et al. 2017). Participants with bipharospasm dystonia were more cautious during the initial adjustment to split belt asymmetry (Hoffland, Veugen et al. 2014).

Four studies found that participants with PD both on and off DOPA medication adapted step length and anterior-posterior ground reaction forces similarly to healthy participants (Nanhoe-Mahabier, Snijders et al. 2013, Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Mohammadi, Bruijn et al. 2015). In two studies, participants with PD and freezing of gait also showed the ability to adapt but not to the same extent, with a greater step length asymmetry and altered temporal gait regulation (Nanhoe-Mahabier, Snijders et al. 2013, Mohammadi, Bruijn et al. 2015). Finally, the study of participants with focal dystonia revealed participants with cervical dystonia showed no difference in the ability to adapt gait to split belts compared to healthy older adults while those with bipharospasm dystonia were slower than healthy older adults (Hoffland, Veugen et al. 2014).

Participants with PD stored aftereffects and demonstrated savings post-adaptation (Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Fasano, Schlenstedt et al. 2016) however, step length aftereffects were diminished off DOPA medications (Roemmich, Hack et al. 2014) and when the more affected leg was slowed (Fasano, Schlenstedt et al. 2016). Participants with bipharospasm dystonia exhibited limited storage of the newly learned gait pattern while those with cervical dystonia were able to show aftereffects similar to healthy older adults (Hoffland, Veugen et al. 2014).

Table 3.3: Investigating the role of the Basal Ganglia

All studies used a variation of the adaptation protocol including an extended exposure to split belts unless specified with ** to indicate short bouts of split belt and tied-belt walking were compared. *DOPA: Dopamine medication; AE: aftereffects*

Author (Year)	Participants	Mean Age±SD	Main Findings
Parkinson's disease (PD)			
38. Dietz et al. (1995) **	14 PD, 10 healthy older	61±11.4; 60.6±6	PD – anterior-posterior kinetics adapt reactively- no storage
39. Roemmich et al. (2014)a	10 PD	49 - 76	On and off DOPA adapted step length similar to healthy; Off DOPA, step length AE was diminished.
40. Roemmich et al. (2014)b	13 PD, 15 young, 15 healthy older	64.1±8.8; 65.2±8.1; 22.3±3.3	On and off DOPA adapted step length similar to healthy; PD stored AE and demonstrated savings.
41. Fasano et al. (2016)	20 PD	60.5±8.8	PD stored AE and demonstrated savings; AE worsened when worse leg was slowed
Parkinson's disease with freezing of gait (PD+FOG)			
42. Nanhoe-Mahabier et al. (2013)	7 PD+FOG; 7 PD; 10 healthy older	64.1±2.3; 62.1±2.7; 62.4±1.7	On and off DOPA adapted step length similar to healthy; PD+FOG differed in temporal gait regulation.
43. Mohammadi et al. (2015)	10 PD+FOG, 12 PD, 12 healthy older	60.4±5.4; 62.5±7.4; 61.9±6.2	On and off DOPA adapted step length similar to healthy; PD stored AE and demonstrated savings; PD+FOG showed largest step length asymmetry
44. Bekkers et al. (2017)	13 PD+FOG, 12 PD, 12 Healthy older	67±7.2; 63±8.6; 65.3±8.3	Freezers were worse at perceiving difference between belts but no difference in threshold.
Focal Dystonia			
45. Hoffland et al. (2014)	26 dystonia, 10 healthy	56.5±8.2; 54.8±7.8	Writer's cramp and Bipharospasm (BSP) dystonia were more cautious; BSP were slower to adapt and no AE in BSP; No effect of cervical dystonia on adaptation or AE.

Role of Central Pattern Generator

Both studies of infants found that infants adjusted both legs to maintain alternating stepping on asymmetric split belts before independent upright stance was present (Thelen, Ulrich et al. 1987, Yang, Lamont et al. 2005). A third study of infants and toddlers also observed their ability to adjust the gait cycle to split belt using a step rate intermediate to that used typically for either of the belts, an increase in time spent in stance on the slow leg and asymmetric gait cycle duration between legs (Musselman, Patrick et al. 2011)

In contrast to the initial gait adjustments to split belts, infants did not demonstrate the ability to adapt the gait pattern to split belts, instead maintaining the same performance throughout exposure to asymmetric belts speeds (Thelen, Ulrich et al. 1987, Yang, Lamont et al. 2005). While the majority of toddlers were able to adapt gait phasing symmetry and step length symmetry, none were able to adapt spatial gait coordination to the split belts indicating temporal and spatial adaptation did not occur at the same time (Musselman, Patrick et al. 2011).

Since adaptation did not occur, infants did not demonstrate savings of the gait pattern used during split belt walking to walking on belts at the same speed (Thelen, Ulrich et al. 1987, Yang, Lamont et al. 2005). When toddlers did adapt a gait parameter (e.g. step length) to split belts, they also demonstrated savings of the newly-learned gait parameter when returning to tied-belts (Musselman, Patrick et al. 2011)

Table 3.4: Investigating the role of Central Pattern Generators

All studies used a variation of the adaptation protocol including an extended exposure to split belts unless specified with ** to indicate short bouts of split belt and tied-belt walking were compared. *SB: split belt; DST: dual support time*

Author (Year)	Participants	Mean Age±SD	Main Findings
Healthy Infants			
46. Thelen et al. (1987) **	8 Healthy Infants	7 months	Infants made adjustments to both legs to maintain alternating stepping, before actual upright stance ; Step rate intermediate to speeds in SB, with asymmetric cycle durations, no change to swing but increase in stance for slow leg; Pattern is responsive to the context, even if only speed from 1 belt changes, both legs changed
47. Yang et al. (2005) **	45 Healthy Infants	9.4±1.3 m	Infants made adjustments to both legs to maintain alternating stepping, before actual upright stance; Step rate intermediate to speeds in SB, with asymmetric cycle durations, no change to swing but increase in stance for slow leg
Healthy Toddlers			
48. Musselman, et al. (2011)	27 Healthy Infants/Toddlers	6 to 36 months	Step rate intermediate to speeds in SB, with asymmetric cycle durations, no change to swing but increase in stance for slow leg; 3/26 children did not adapt DST while 7/19 children did not adapt step length and 0 adapted centre of oscillation (spatial coordination)- temporal and spatial adaptation did not occur at the same time

Role of Sensory Feedback

The majority of manipulations to sensory feedback in healthy participants did not affect the initial gait adjustments to split belt treadmill walking. However, altered proprioceptive feedback, via lower limb muscle stimulation, demonstrated the greatest effects to gait control during this period. One study found inadvertent activations of tibialis anterior (dorsiflexion) decreased during early to mid-stance (a period of limb loading) and end swing (a period of load preparation) during split belt treadmill walking (Duysens, Bastiaanse et al. 2004).

Manipulation of proprioceptive and visual feedback affected the control of gait adaptation to split belts. For instance, accurate visual feedback of the gait pattern during split belt walking reduced asymmetry in late adaptation (Leech, Day et al. 2018). In addition, a mirror placed in frontal plane reduced stance time asymmetry and variability during the later stages of adaptation (Stone, Terza et al. 2019). There was, however, no effect of visual feedback on the magnitude of asymmetry during adaptation (Eikema, Chien et al. 2016, Leech, Day et al. 2018), even when distorted from proprioceptive information (Chunduru, Kim et al. 2019).

In contrast, adaptation in healthy participants occurred unaltered no matter if told how to adapt or prevented from adapting (Roemmich, Long et al. 2016). Knee and hip joint range of motion can be adapted and stored simultaneously, and without interference, to split belt adaptation (Statton, Toliver et al. 2016). There is also evidence that a "straight ahead" mechanism of visual input controls split belt adaptation rather than direct vestibular input (Marques, Colombo et al. 2007). Furthermore, the magnitude and timing of vestibular contribution to each limb during split belt adaptation was similar to velocity-matched tied-belt walking (at a fixed cadence) (Forbes, Vlutters et al. 2017). Finally, there was no effect of vibration on initial split belt adjustments (Layne, Chelette et al. 2015, Mukherjee, Eikema et al. 2015).

Table 3.5: Investigating the Role of Sensory Feedback

All studies used a variation of the adaptation protocol including an extended exposure to split belts unless specified with ** to indicate short bouts of split belt and tied-belt walking were compared. *SB: split belt; TB: tied-belt*

Author (Year)	Participants	Mean Age±SD	Main Findings
Healthy with altered body weight			
49. Jensen et al. (1998)**	10 Healthy	25±4.6	Reduced AE (i.e. storage) when body weight was not their own
Healthy with muscle stimulation			
50. Duysens et al. (2004)	Not Provided	-	Increase in TA activity during SB, suppressed with stimulation – inadvertent activations of TA avoided during early to mid stance (limb loading) and end swing (load preparation)
Healthy with visual feedback			
51. Marques et al. (2007)	12 Healthy	24-35 years	"Straight ahead" mechanism of visual input controls SB walking (slow velocity) rather than direct vestibular input
52. Torres-Oviedo et al. (2010)	E1: 23 Healthy; E2: 16 Healthy	25.2±4.9; 23±5.9	Removing context-specific visual cues increased learning, transfer and washout (i.e. removing vision during over ground) but removing vision during adaptation did not improve transfer
53. Finley et al. (2014)	57 Healthy	24±4	Optic flow influences the swing phase in preparation for the next step.
54. Eikema et al. (2016)	20 Healthy	26.2±4.9	Visual Feedback - No effect of visual feedback on amount of asymmetry during adaptation or initial re-adaptation
55. Leech et al (2018)a	40 Healthy	24±4	Visual Feedback - No effect of visual feedback on amount of asymmetry during adaptation or initial re-adaptation, Visual feedback reduced asymmetry in late adapt
56. Chunduru et al. (2019)	23 Healthy	18-30	Visual Feedback - No effect of visual feedback on amount of asymmetry during adaptation or initial re-adaptation, even when distorted from proprioceptive information
57. Stone et al (2019)	40 Healthy	21±3	Mirror in frontal plane reduced stance time asymmetry and reduced aftereffects, reduced variability in late adaptation
Healthy with vestibular stimulation			
58. Forbes et al. (2017)	16 Healthy	27±4	Magnitude and timing of vestibular contribution to each limb during steady-state SB was similar to velocity match TB (fixed cadence); Vestibular-motor response magnitude to SB established faster than adaptation for SLS or muscle activity. No AE (storage) for vestibular muscular coupling
Healthy with plantar vibration			
59. Layne et al. (2015)	10 Healthy	26.7±4.3	No effect of vibration.
60. Mukherjee et al. (2015)	20 Healthy	26±5.4	No effect of vibration.
Healthy with movement feedback			

Author (Year)	Participants	Mean Age±SD	Main Findings
61. Roemmich et al. (2016)	E1: 20 Healthy; E2: 20 Healthy; E3: 20 Healthy; E4: 9 Healthy	23±4; 24±4; 27±3; 24±5	Voluntary movement correction is separate from adaptation; Adaptation occurred unaltered no matter if told how to adapt or prevented from adapted, AE (storage) is robust
62. Statton et al. (2016)	E1: 18 Healthy; E2: 27 Healthy	26±4; 24±4	Knee/Hip joint ROM can be adapted and stored (AE) simultaneous and without interference with SB adaptation

The degree to which healthy adults demonstrated savings was affected by sensory feedback manipulation. For instance, when participants' body weight was altered via weighted best or body weight support, they had reduced storage of the newly learned gait pattern (Jensen, Prokop et al. 1998). Accurate real-time visual feedback of the gait pattern with a mirror reduced aftereffects (Stone, Terza et al. 2019). However, there was no effect of visual feedback on the magnitude of asymmetry during initial de-adaptation, the time demonstrating the magnitude of initial savings (Eikema, Chien et al. 2016, Leech, Day et al. 2018).

3.5 Discussion

This systematic review of the literature consolidates the key hypotheses to date explaining the role(s) of the CNS in adapting the human motor system to the symmetry perturbation induced by a split belt treadmill. Based on the 62 studies identified, we propose distinct roles for the human CNS in 1) the initial gait adjustments required for walking on belts at different speeds and 2) the adaptation and 3) storage of a new gait pattern appropriate for walking on the split belt treadmill (Figure 3.2). From studies of infants, and manipulation of sensory feedback in healthy adults, we suggest that the initial gait adjustments to walking on belts at different speeds will have the greatest reliance on proprioceptive feedback to immediately inform central pattern generators to the nature of the initial adjustments to muscle pattern output to adjust stance and swing. Concurrent to these initial adjustments, we suggest that sensory feedback from proprioceptive and visual information will inform cerebral and cerebellar regions related to motor planning and motor output to adapt and store a gait pattern that is biomechanically and metabolically efficient to walk on belts at different speeds. Finally, evidence from participants post-stroke and with cerebellar lesions suggest that the location for storage of the newly learned walking pattern is not completely reliant

on either of these brain areas but that injury to either area can affect the ability to store the gait pattern.

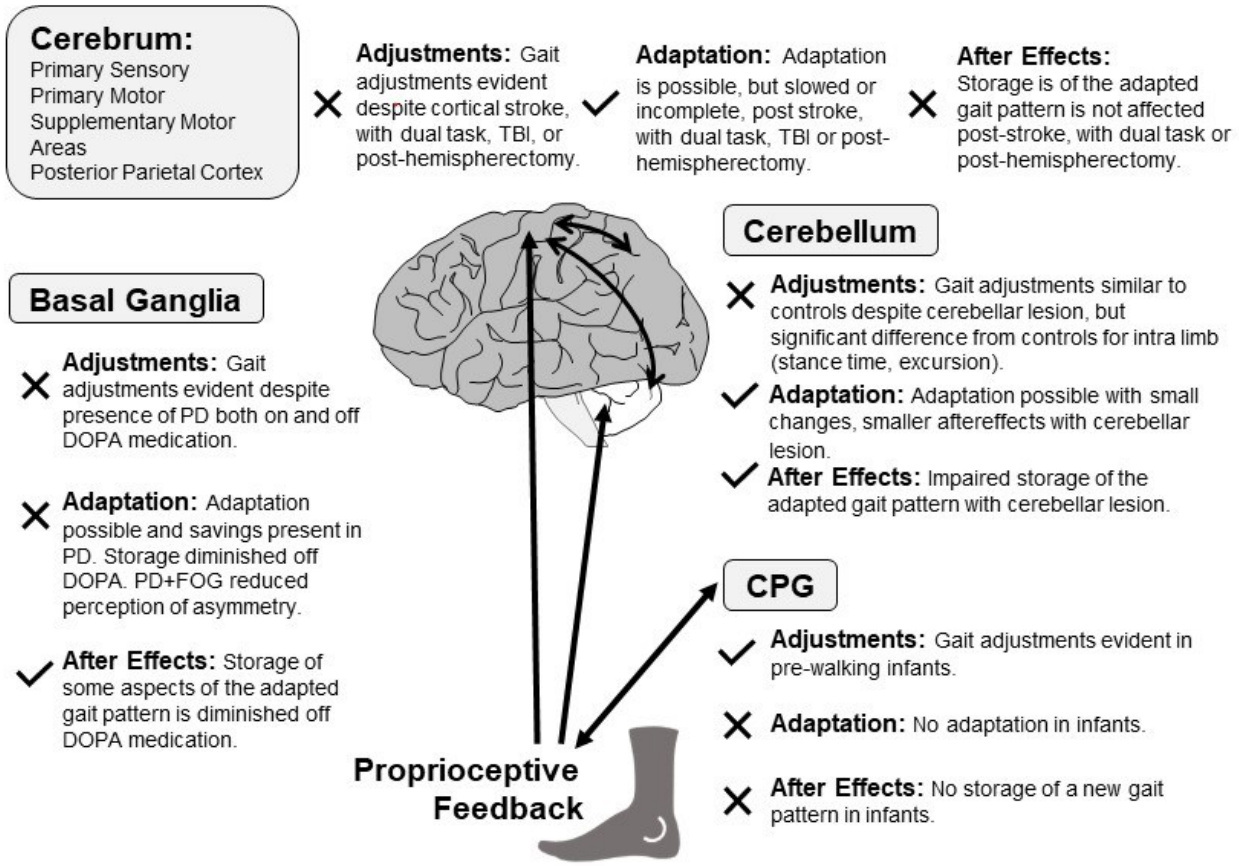

Figure 3.2: Proposed sites of gait adjustments and adaptation to the split belt treadmill and storage of the adapted gait pattern in the human central nervous system.

Initial adjustments to split belts

Evidence from infants and toddlers stepping on a split belt treadmill prior to independent or mature walking patterns support the hypothesis that CPG's and proprioceptive feedback have a strong role in the control of the initial adjustments to split belt treadmill walking. At this stage of development, when infants can not yet walk independently, supraspinal control of posture and gait

will not yet have its full influence on the neural control of walking. Therefore, the study of infants prior to independent walking on a split belt treadmill is hypothesized to provide evidence of the role of CPGs and the influence of proprioceptive information in accommodating the split belt treadmill into locomotion. CPGs are spinal interneuronal networks that generate rhythmic activity in the absence of supraspinal input (Rossignol 2006, Rossignol 2010, Frigon 2012). Infants who were supported over top of the treadmill were able to produce the same characteristic gait pattern of stance and swing immediately upon experiencing belts at different speeds (Thelen, Ulrich et al. 1987, Yang, Lamont et al. 2005).

In addition, immediate changes to step rate were evident in healthy infants prior to walking with step rate intermediate to both belt speeds in split belt, asymmetric cycle durations and an increase in stance for leg on slow belt (Thelen, Ulrich et al. 1987, Yang, Lamont et al. 2005, Musselman, Patrick et al. 2011). Finally, the infants' gait pattern is responsive to the context, even if only speed from one belt changes, both legs changed indicating that proprioceptive information is informing gait pattern changes to both legs (Thelen, Ulrich et al. 1987). While infants can adjust their gait pattern appropriately to the conditions of split belts, there is no evidence of storage or adaptation in infants or toddlers with extended exposure to split belts. This supports the hypothesis that the immediate changes to the gait pattern produced by CPGs are reactive in nature and not directly involved in the adaptation process or storage of a more efficient walking pattern on split-bets.

Gait adaptation to split belts: role of sensory feedback

In addition to immediate step-to-step changes that would be occurring to accommodate the initial change in belts speeds, there are ongoing feedback systems incorporating visual, proprioceptive, vestibular information into the ongoing locomotor plan. Evidence suggests that

voluntary movement correction, or adjustments that occur rapidly upon exposure to split belts, is controlled separately from adaptation process whereby the gait pattern becomes more efficient and this new gait pattern is stored (Roemmich, Long et al. 2016). The various types of sensory feedback have different effects during adaptation to the split belt treadmill. Proprioceptive information is used in a phasic manner to determine if and when the foot can safely transition from swing to stance and activate the appropriate response from a CPG for the next step to take place (Pearson 2004). Whereas visual information, in the form of optic flow on a treadmill, that was matched to the speed of the stance leg adapted the most quickly (Finley, Statton et al. 2014). The importance of proprioceptive and environmental cues drawn from the stance phase, especially on a treadmill, will provide the most up to date information on the efficiency of the stepping pattern.

Gait adaptation to split belts: role of the cerebellum

Adaptation has been primarily hypothesized to be associated with activity within the cerebellum (Bastian 2006, Morton and Bastian 2006, Malone and Bastian 2010, Jayaram, Galea et al. 2011, Jayaram, Tang et al. 2012, Malone, Bastian et al. 2012, Malone and Bastian 2014). However, evidence from participants with cerebellar degeneration or lesion(s) suggest there does not seem to be a strong role of the cerebellum in the control of the initial adjustments to split belt treadmill walking (Morton and Bastian 2006, Hoogkamer, Bruijn et al. 2015). Differentiating the initial adjustments to split belts from the process of adaptation to split belts is the integration of step to step error(s) into updating the gait pattern. In line with this model, with each step, the cerebellum integrates sensory and motor feedback and aids in planning for the next step. During split belt treadmill adaptation this would incur gradual changes to ongoing gait symmetry to optimize the walking pattern to asymmetric belt speeds. Indeed, the cerebellum is a hub of confluent information including sensory feedback from this periphery (i.e. proprioceptive

information from the lower limbs) and cortical regions including the primary motor areas (Takakusaki 2013).

In contrast to the initial gait adjustments to the split belt treadmill damage within the cerebellar hemispheres has been shown to make adaptation of gait adaptation to asymmetric belt speeds difficult (Morton and Bastian 2006). While performance of participants with cerebellar lesions is not affected for gait outcomes related to interlimb coordination (i.e. step length), there are significant differences between participants with cerebellar lesions from healthy controls for intralimb parameters (stance time and excursion) (Hoogkamer, Bruijn et al. 2015). Cerebellar patients displayed more asymmetric baseline walking patterns, with the most asymmetric patients having lesions in vermal lobules VI and crus II (Hoogkamer, Bruijn et al. 2015). Via the pontine and dentate nuclei, the primary motor cortex and cerebellar lobule VI exchange information, pointing to this area's role in sensorimotor integration and movement error (Glickstein, May III et al. 1985, Kitazawa, Kimura et al. 1998, Imamizu, Miyauchi et al. 2000, Kelly and Strick 2003, Diedrichsen, Hashambhoy et al. 2005). This area of the cerebellum has also been hypothesized as part of a fine-tuning network while adjusting walking to the split belt treadmill (Hinton, Thiel et al. 2019). It appears the cerebellum does have a role in adapting the gait pattern to the split belt treadmill however it is not completely reliant on this region for partial adaptation of some gait parameters.

Gait adaptation to split belts: role of cerebral control

The role of specific cortical areas during split belt treadmill adaptation is difficult to ascertain. In human split belt walking, we rely on evidence from adult's post-stroke, traumatic brain injury, or cerebral palsy or participants who performed a simultaneous dual task. For participants with cortical stroke, retention and transfer of a newly learned split belt pattern to

overground walking was possible indicating that complete cortical areas may not be required for retention of a newly learned walking pattern (Reisman, Wityk et al. 2009, Charalambous, Alcantara et al. 2018). While a secondary task (cognitive and/or motor) did not affect stride timing or variability during split belt walking (McFadyen, Hegeman et al. 2009, Hinton, Cheng et al. 2018, Vervoort, den Otter et al. 2019) or sagittal inclination angle or variability (Sawers, Kelly et al. 2013), a cognitive-based secondary task did increase dual support phase indicating asymmetric gait may require attention due to increased dynamic balance requirements (McFadyen, Hegeman et al. 2009). Even children post-hemispherectomy show adjustments and adaptation of the gait pattern to split belts, bringing into question the full requirements of cortical areas for this process (Choi, Vining et al. 2009).

A limitation to human clinical populations, such as participants post-stroke, is the heterogeneity of lesion location. Among the studies identified for this review, a wide variety of lesion location was noted, with only a few studies limiting their participants to those without lesions in the cerebellum. In doing so, we can only glean a general hypothesis of cortical control during split belt adaptation. In contrast, animal models of treadmill walking have provided more detail to the exact cortical locations required for gait adaptation. For example, based on single cell recordings of the walking cat, the PPC has been hypothesized to be used for integrating tactile and visual information with motor output for the upcoming step during obstacle avoidance while walking (Lajoie, Andujar et al. 2010, Marigold and Drew 2011, Drew and Marigold 2015, Wong and Lomber 2018). Use of the PPC during split belt adaptation aligns with its proposed function in integrating limb movements and environmental information to create and update a body schema (Takakusaki 2013). Indeed, imaging of human brain metabolism observed increased activity in the

PPC while walking with continuous turns overground (Mitchell, Starrs et al. 2018, Mitchell, Potvin-Desrochers et al. 2019) or speed changes on a split belt treadmill (Hinton, Thiel et al. 2019).

Brain stimulation via tDCS or TMS provides more specific modulation of brain networks, that when altered, can provide insight into the use of these areas during a motor task. The brain stimulation studies found during this review were focused on the primary motor area and cerebellum and found the adaptation process decreased the normal inhibitory tone from cerebellum to primary motor area. Further supporting the role of cortical areas during adaptation. In support of the primary motor area, and the aforementioned sensory integration requiring the use of the PPC, motor planning areas would also likely be involved. Studies utilizing brain imaging during treadmill walking have hypothesize that the supplementary motor area (SMA) is involved in locomotor planning and maintaining rhythmic stepping (Fukuyama, Ouchi et al. 1997, Harada, Miyai et al. 2009, Gwin, Gramann et al. 2011). In addition, increased anterior cingulate cortex (ACC) activity has been observed during foot placement monitoring and ongoing error correction (Bush, Luu et al. 2000, Gwin, Gramann et al. 2011). Finally, brain imaging of brain metabolism during continuous belt speed changes on a split belt treadmill also indicated SMA and ACC activations are required for fine-tuning the stepping pattern in response to a change to the belt speed ratio (Hinton, Thiel et al. 2019). While the use of broad clinical populations (i.e. post stroke, TBI or post-hemispherectomy) or cognitive dual tasking cannot provide a more specific hypothesis of the cortical control of gait adaptation to split belt walking, it supports hypotheses from other animal and human walking studies of the cortical involvement during complex walking.

Gait adaptation to split belts: role of basal ganglia

The structures of the basal ganglia are responsible for producing smooth coordinated movements. Through disinhibition of locomotor regions in the brain stem, the basal ganglia evokes

walking behavior (Grillner 2003, Rossignol 2010). Adults with Parkinson's disease typically exhibit jerky movements, tremor and trouble producing a smooth walking pattern due to a lack of dopamine being produced and circulated by the basal ganglia (Alexander, Crutcher et al. 1990, Buhmann, Glauche et al. 2003). However, the altered dopamine processing due to Parkinson's disease did not have a strong effect on the control of the initial adjustments or adaptation to split belt treadmill walking. While there was an impaired perception of belt speeds in adults with PD and freezing of gait (Bekkers, Hoogkamer et al. 2017), adults with PD (both with and without freezing of gait) could adapt to walking with belts at different speeds (Nanhoe-Mahabier, Snijders et al. 2013, Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Mohammadi, Bruijn et al. 2015). The basal ganglia is hypothesized to be integrating automatic processes of posture and movement (i.e. activating basic locomotor patterns) with cortical control of volitional changes (Takakusaki, Saitoh et al. 2004) that could be involved in split belt adaptation. Brain imaging of the basal ganglia during walking typically shows an increase in activation compared to rest (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999, Ouchi, Kanno et al. 2001) but more recently saw no change in activation of the caudate and putamen during typical straight walking compared to lying down (la Fougere, Zwergal et al. 2010). In addition, there was an increase in activation of basal ganglia, with premotor cortical areas, during imagined modulation of the walking plan (la Fougere, Zwergal et al. 2010). Aligning with the findings of this review that basal ganglia will aid in the modulation of the gait pattern required for split belt treadmill adaptation, participants with PD and freezing of gait (i.e. more severe inhibition of the basal ganglia) differed from those without freezing of gait in temporal gait regulation (Nanhoe-Mahabier, Snijders et al. 2013) and showed the largest step length asymmetry (Mohammadi, Bruijn et al. 2015).

3.6 Conclusion

This systematic review of the literature consolidated the key hypotheses for the various roles of the human CNS in adjusting and adapting gait to the split belt treadmill. From the studies identified in this review, we propose that initial gait adjustments required to walk on split belts are reliant on proprioceptive feedback that will inform central pattern generators to immediately adjust muscle pattern output for the appropriate changes to stance and swing. Evidence from clinical populations affecting cerebellar and cerebral control of walking do not suggest a strong influence of these supraspinal centres in the control of the initial gait adjustments to asymmetric split belts. Simultaneous to this gait adjustments, we propose that evidence across a variety of clinical populations suggests the locomotor plan is attempting to continuously incorporate sensory and motor feedback to inform cerebral (i.e. motor, supplementary motor and parietal cortices) and cerebellar regions to adapt and store a new and efficient gait pattern to walk on belts at different speeds.

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PREFACE: Chapter 4

Split-belt walking has cerebral requirements that range from the prefrontal cortex to the premotor and motor planning areas, all of which overlap with potential cerebral requirements of walking and split belt treadmill adaptation. From my systematic review, I understood that different regions of the central nervous system are involved in different aspects of the adaptation process. For instance, based on evidence from clinical populations affecting cerebellar and cerebral control of walking, I did not hypothesize a strong influence of these supraspinal centres in the control of the initial gait adjustments to asymmetric split belts. Instead, I hypothesized that initial gait adjustments required to walk on split belts are reliant on proprioceptive feedback. Simultaneous to this gait adjustments, I proposed that evidence across a variety of clinical populations suggests that the locomotor plan is attempting to continuously incorporate sensory and motor feedback to inform cerebral (i.e. motor, supplementary motor and parietal cortices) and cerebellar regions to adapt and store a new and efficient gait pattern to walk on belts at different speeds. From this review however, it was not yet well understood the specific role of prefrontal cortical areas in this process. While some studies did employ a cognitive task to assess the role of executive function in the adaptation process, the results were mixed and not specific.

The first experimental study of this thesis aimed to identify the cognitive influence on gait adaptation to split belt treadmill and the shared neural substrates between a working memory task and split belt treadmill adaptation in young healthy adults Using dual-task methodologies, the relative change in cognitive input to carry out locomotor adaptation will be estimated. The auditory n-back task was administered during different parts of the split belt adaptation period (i.e. during the initial adjustment phase, or once participants have been able to begin the adaptation period) to assess how cognitive resources are allocated in healthy young adults during split belt walking.

Chapter 4: Does dual task placement or duration affect split belt treadmill adaptation?

THESIS STUDY 2

Authors: Dorelle C. Hinton[1,2], David Conradsson[1,3], Laurent Bouyer[4], Caroline Paquette[1,2*]

Affiliations:

[1] Department of Kinesiology & Physical Education, McGill University, Canada

[2] Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR)

[3] Department of Neurobiology, Health Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Sweden

[4] Center for Interdisciplinary Research in Rehabilitation and Social Integration, Laval University, Canada

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4.1 Abstract:

Background: Dual tasking during prolonged split belt adaptation (10-15 min) has shown to slow the adaptation process and prolong aftereffects. Therefore, dual tasks during split belt adaptation are being explored for their potential in gait symmetry rehabilitation. However, the ideal paradigm configuration it is still not clear.

Research Question: To determine whether split belt adaptation and ensuing aftereffects are altered by dual task placement, specifically looking at onset of split belt adaptation or later part way through Adaptation (Experiment 1) and dual task duration (Experiment 2).

Methods: Healthy young adults (n=40) performed 5 minutes of tied-belt walking, followed by 14 minutes of split belts (Adaptation, 1:3 ratio) and 5 minutes of de-adaptation (both belts at same speed) to assess aftereffects (Post-Adaptation). Experiment 1: To assess the effects of dual task placement, an auditory version of an n-back task was presented during the first 8 minutes or last 8 minutes of Adaptation. Experiment 2: To assess the effects of dual task duration, the cognitive task was presented during the entire split belt Adaptation phase (14 minutes) or during four 2-minute bouts (8 minutes). Cognitive task accuracy, dual support symmetry, and rates of adaptation and de-adaptation were compared.

Results: When both the onset of the auditory cognitive task and the onset of Adaptation (split belts) occurred simultaneously, participants prioritized split belt adaptation and in doing so, cognitive task accuracy was reduced (Experiment 1). By prioritizing gait symmetry over cognitive performance, there were no differences in dual support symmetry adaptation (magnitude, variability or rate of Adaptation/De-adaptation) regardless of cognitive task placement or duration (Experiment 2).

Significance: We believe the early portion of split belt treadmill adaptation to be a cognitive interference period. These results support future work exploring the use of dual task in a rehabilitation setting with more complicated motor-cognitive dual task paradigms during this key period.

4.2 Introduction

Every day, the way we walk must be adapted to our surroundings to avoid falling and to maintain an efficient stepping pattern. For instance, we require a diverse set of walking patterns with alterations to both spatial (e.g. step length) and temporal (e.g. dual support timing) aspects of gait to navigate our environment. In the laboratory, a split belt treadmill, with independently driven belts beneath each foot, allows for the study of gait adaptation to asymmetric belt speeds. During split belt adaptation, feedforward anticipatory gait control gradually allows participants to create a new context-specific locomotor program (Blanchette and Bouyer 2009, Reisman, Bastian et al. 2010) primarily focused on interlimb coordination such as gait phasing (Reisman, Block et al. 2005, Morton and Bastian 2006, Choi, Vining et al. 2009, Reisman, Bastian et al. 2010). Upon return to tied-belts, the newly-learned gait pattern must be *un*-learned to return to the typical walking pattern.

Previous dual task literature has determined a change in attentional allocation occurs while split belt walking. For instance, during short bouts of walking, responding to an auditory Stroop task increased time spent in dual support during split belt walking compared to typical treadmill walking (McFadyen, Hegeman et al. 2009). Similarly, with the addition of a visually-presented reaction time task to split belt walking, participants increased reaction time while adapting to walk

with split belts without a detriment to gait performance (Sawers, Kelly et al. 2013). These changes in attentional resources were confirmed by Sawers and colleagues, where split belts were introduced either suddenly or more gradually with incremental belt speed changes (Sawers, Kelly et al. 2013). Participants increased dual task reaction time when the split belt perturbation occurred suddenly, calling into consideration the more specific effects of split belt onset on attention (Sawers, Kelly et al. 2013).

Both split belt adaptation and dual tasking are being explored for their potential in rehabilitation of a neurologically-based gait asymmetry (Malone and Bastian 2010, Reisman, Bastian et al. 2010, Malone, Vasudevan et al. 2011, Reisman, McLean et al. 2013, Sawers, Kelly et al. 2013, Lewek, Braun et al. 2018). For instance, with an audio-visual distraction task during split belt treadmill adaptation, the adaptation *and* de-adaptation processes can be slowed, emphasizing the potential for dual task paradigms to prolong the training effects of split belt adaptations (Malone and Bastian 2010). To date, dual tasking during split belt adaptation typically occurs across the entire adaptation protocol (10 to 15 minutes), however the ideal paradigm configuration it is still not clear.

Our first study objective (*Experiment 1)* identified whether split belt adaptation and ensuing aftereffects change with dual task placement at the beginning or ending of adaptation. We predicted adaptation to the split belt treadmill would still be possible but dual task onset coinciding with split belt adaptation would induce greater detriments to cognitive task accuracy compared to dual task onset when split belt gait adaptation has already been established.

As a cognitive dual task, the n-back task is a complex dual task widely used to study working memory, requiring active maintenance of multiple stimuli in immediate memory and adjustment of behaviour in response to feedback (Cohen, Forman et al. 1994, d'Esposito, Aguirre

et al. 1998). Given that cognitive dual tasks combined with split belt treadmill adaptation may have a future role in gait rehabilitation, multiple paradigm configurations are possible. However, it is unknown whether altering the dual task duration would affect the split belt adaptation process or ensuing aftereffects. As such, our second study objective (*Experiment* 2) compared participants who had the dual task throughout adaptation or in intermittent bouts. Given changes to attention allocation during split belt adaptation occur as soon as split belt onset occurs, we hypothesized that participants with intermittent bouts of dual task would still incur the same aftereffects as those with dual tasking throughout Adaptation.

4.3 Methods

Participants

Forty healthy, young adults (17 males, mean age ± standard deviation (SD): 23±2 years) with normal or corrected-to-normal vision and no history of vestibular dysfunction, neurological disorders or musculoskeletal disorders participated in this study. Participants were not on medication that alters mood, alertness or ability to concentrate and provided written informed consent. The experimental protocol was approved by the McGill Institutional Review Board.

Protocol

Participants walked on a dual belt treadmill (Forcelink Dual Belted Treadmill on N-Mill Frame) consisting of two independently operated belts with a 5 cm gap and three safety bars (front, right-, left-hand sides). While walking, participants wore a safety harness that provided no mechanical support nor hindered movements and was only engaged in the case of a fall, none of which occurred. Kinematic data was collected using seven wireless inertial sensors (Opal^{TM},

APDM Inc., Portland, OR) positioned on the forehead, sternum, sacrum, left and right wrist, and left and right lower shank and continuously streamed to a computer with Mobility Lab^{TM} software (iWalk plugin, APDM Inc., Portland, OR).

All participants performed a 24-minute walking trial that included both tied belt (belts driven at same speed) and split belt walking (belts at differing speeds; Figure 4.1). To determine baseline walking speed, prior to the walking trial, tied belt speeds were increased incrementally (0.08 m/s) from standing until the participant perceived the speed to correspond to their comfortable speed during overground walking. Participants walked with arms swinging naturally at their sides and their gaze directed towards a marked 10X10cm 'X' on the wall positioned at the subject's eye level, one meter ahead of the treadmill.

After 5 minutes of tied-belt walking (mean±SD: 0.8±0.1 m/s), the belt driving the dominant leg (n=35 right footed determined via Waterloo Footedness Questionnaire, Elias, Bryden et al. 1998) was decreased to one third of the original walking speed for 14 minutes (Adaptation, mean ±SD: 0.3±0.1 m/s) and then returned to tied-belt walking (Post-Adaptation). Warnings or verbal feedback of upcoming belt speed changes were not provided.

The cognitive dual task (a modified auditory version of the n-backer task, Monk, Jackson et al. 2011) required participants to listen to a series of randomly presented, single-syllable digits (1 through 10, without 7) and after each, verbally respond as quickly and accurately as possible with the digit from two before it in the sequence (n-back = 2-back, Baddeley 1992, Gevins and Cutillo 1993). Digits were presented every 2 seconds (±0.1 seconds) through binaural over-ear headphones and never repeated twice in a row. Participants were told not to respond to the first two digits and begin responding on the third digit, with a correct response possible on all remaining digits. The same sequence of digits was presented to each participant. Participants practiced the

auditory cognitive task in a seated posture followed by standing; the latter used as baseline DT performance.

Participants were randomly allocated to one of 4 groups and completed a single split belt Adaptation protocol with the cognitive task on one occasion (Figure 4.1).

Experiment 1: To assess whether dual tasking placement during adaptation affects adaptation and de-adaptation, 21 of 40 participants were randomly allocated to:

First Half (n=10): dual task during the first 8 minutes.

Second Half (n=11): dual task during last 8 minutes.

Experiment 2: To assess whether dual task duration affects the magnitude or rate of gait adaptation, 19 of 40 participants were randomly allocated to:

Complete (n=9) dual task during the entire SB Adaptation phase (14 minutes).

Intermittent (n=10) dual task for four two- minute bouts (8 minutes total).

Participants were not instructed on prioritization between the cognitive and walking tasks and were told to continue to walk as they answered the cognitive task as quickly and accurately as possible.

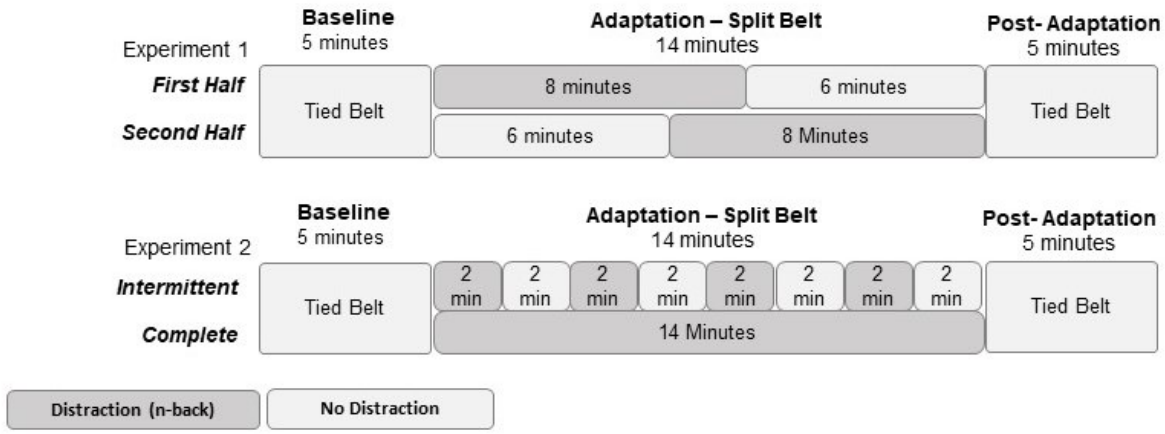

Figure 4.1: Split belt protocol. *Participants were randomly assigned to one of 4 experimental groups differing only in Adaptation period. Dark shaded areas represent periods with the auditory cognitive task.* ***Experiment 1*** *– Dual task placement, participants in the First Half group had the onset of split belts and onset of the cognitive task coincide. Participants in the Second Half group had the onset of the cognitive task occur midway through Adaptation. Both groups were exposed to 8 minutes of distraction during Adaptation (total 14 minutes).* ***Experiment 2*** *– Dual task duration, participants in the Intermittent group were exposed to the cognitive task in two-minute blocks alternating with two minutes without the task. Participants in the Complete group were exposed to the cognitive task throughout the Adaptation period.*

Outcome Measures

Gait adaptation was assessed using the proportion of gait cycle spent in dual support which was separated based on which leg was in terminal stance: right leg dual support occurred from left heel contact to right toe off and vice versa for the left leg (Reisman, Block et al. 2005). Dual support symmetry (DSS) was calculated via Equation 1 (Malone and Bastian 2010). Symmetry values ranged from -1 to 1 where a value of 0 indicates that metrics for both legs are identical. A positive symmetry value indicates longer dual support of the non-dominant (fast) leg and a negative symmetry value indicates the opposite (Malone and Bastian 2010).

Equation 1:

$$Symmetry = \frac{Fast\ Leg - Slow\ Leg}{Fast\ Leg + Slow\ Leg}$$

DSS and DSS SD during the last 60 seconds of tied-belt walking were subtracted from all other strides such that 0 represented the normalized baseline performance for each measure. Group means of DSS and DSS SD were calculated in bins across the Adaptation and Post-Adaptation phases: Initial Adaptation (first 5 strides), Late Adaptation (last 30 strides) and Initial Post-Adaptation (first 5 strides).

The rates of DSS Adaptation and De-Adaptation to split belts were assessed for each subject as the number of strides required for DSS to return to within one SD of the mean symmetry of the last 30 strides in Adaptation or Post-Adaptation and remain within 1 SD for ≥5 consecutive strides.

Mean accuracy (% correct responses based on total possible correct responses) of the cognitive task was calculated where wrong or absent responses were deemed inaccurate. Group means of cognitive task accuracy were calculated for 2 minutes of standing baseline (58 correct responses possible), and first 30 seconds (13 possible responses split into 10 second segments) and last 30 seconds of cognitive task exposure (15 correct responses possible).

Statistical Analysis

All statistical tests were performed in SPSS Version 22 (IBM Corp., Armonk, NY, USA) and significance level was set at 0.05. Data are presented as mean values and standard errors (SE).

Experiment 1 Gait Performance: To assess the effects of dual task placement on DSS and DSS variability, a mixed ANOVA analyzed the effects of group (First Half vs Second Half) and

time (Initial Adaptation, Late Adaptation and Initial De-Adaptation). To assess the effects of dual task placement on rate of DSS Adaptation and De-Adaptation, a one-way ANOVA analyzed for an effect of group (First Half vs Second Half).

Experiment 2 Gait Performance: The same ANOVA's were repeated to assess for the effects of dual task duration on DSS and DSS variability and rate of rate of DSS Adaptation and De-Adaptation (Intermittent vs Complete).

Experiment 1 and 2 Cognitive Performance: To assess for differences in cognitive performance, a mixed analysis of variance (ANOVA) analyzed the between group effects of dual task onset at split (First Half, Complete, Intermittent) or during Adaptation (Second Half) and repeated time points (Baseline, 0-10 seconds, 11-20 seconds, 21-30 seconds, Last 30 seconds).

4.4 Results

Experiment 1: Dual Task placement

Gait Performance: Despite being distracted with the cognitive task, the First Half group's locomotor adaptation to the split belt treadmill was unaffected as they did not demonstrate any change in magnitude of DSS, DSS variability or rate of Adaptation/De-Adaptation compared to the Second Half group, who had the DT start partway through Adaptation (Figure 4.3 A-C; $p>0.05$).

Cognitive Performance: During the initial 10 seconds of cognitive task performance (3 correct responses possible), participants who were also completing the first 10 seconds of split belt exposure had significantly reduced cognitive task performance compared to the Second Half group who did not ($F(4,152)=2.442$, $p<0.05$, Figure 4.2). The Second Half group did not experience this

initial decline in cognitive accuracy when presented with the cognitive task midway through split belt Adaptation: there was no significant change in cognitive task accuracy across Adaptation compared to baseline and was maintained until the end of the cognitive task presentation ($p>0.05$).

Experiment 2: Dual Task duration

Gait Performance: Both Intermittent and Complete groups walked on the split belt treadmill similarly as they did not demonstrate any differences in magnitude of DSS, DSS variability or rate of Adaptation/De-Adaptation (Figure 4.4 A-C; $p>0.05$).

Cognitive Performance: There were no significant differences in cognitive performance between Intermittent and Complete groups.

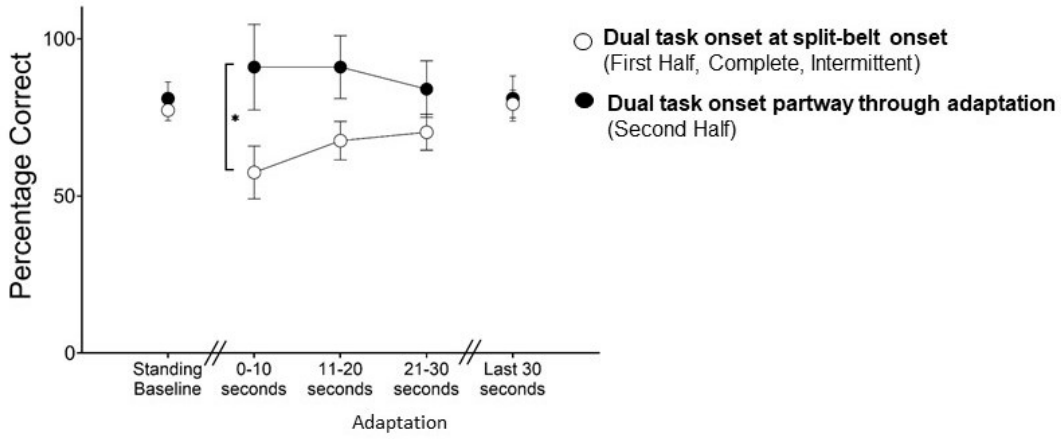

Figure 4.2: Effect of cognitive task onset on cognitive task accuracy*. Conditions differed based on whether the start to the cognitive task coincided with the start of split belts (in white) or partway through the Adaptation process (in black). Data are presented as mean values and standard error.*

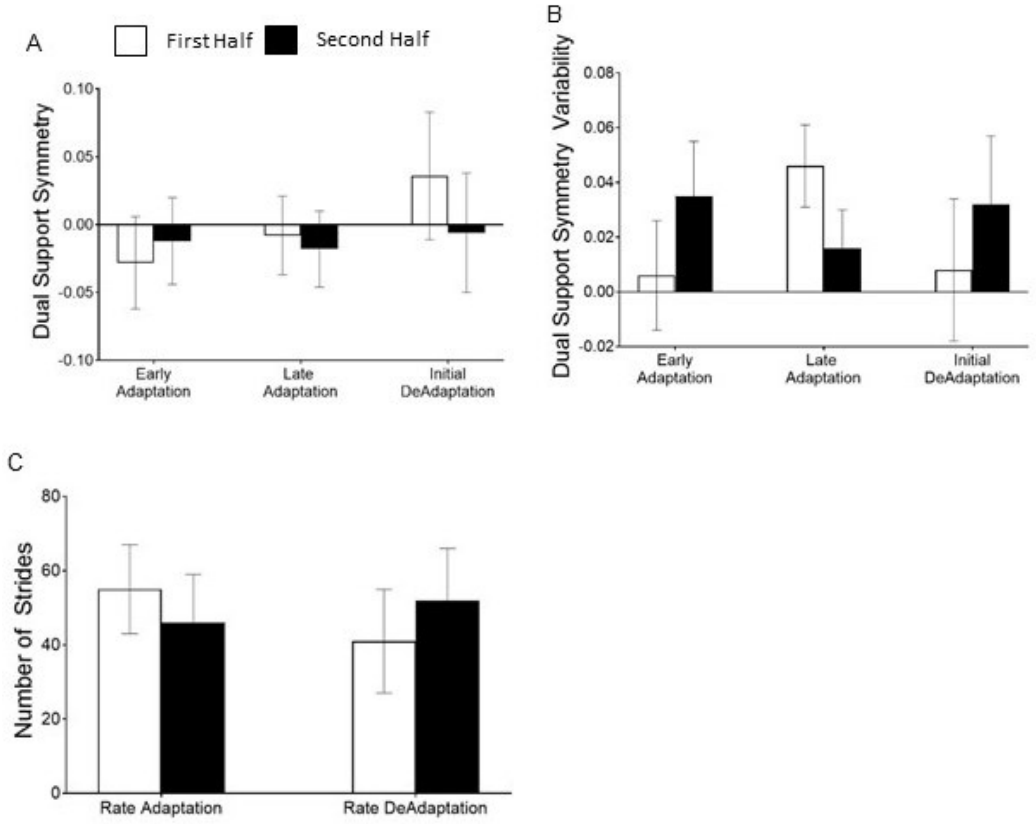

Figure 4.3: Experiment 1- Effect of cognitive task placement of on gait symmetry. *Conditions differed based on whether the start to the cognitive task coincided with the start of split belts (First Half in white) or partway through the Adaptation process (Second Half in black). Data are presented as mean values and standard error.* ***A) Magnitude of Dual Support Symmetry****: A value of 0 represents baseline symmetry during tied belt walking.* ***B) Variability of Dual Support Symmetry.*** *A value of 0 represents baseline variability during tied belt walking.* ***C) Rate of Symmetry Adaptation and De-Adaptation.***

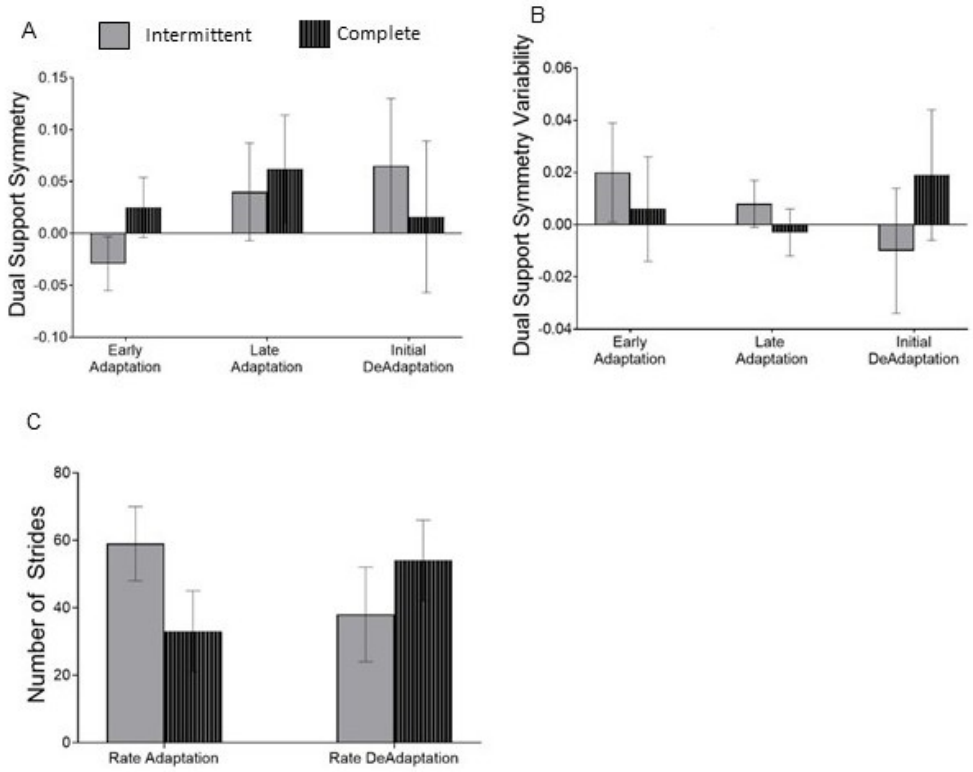

Figure 4.4: Experiment 2- Effect of cognitive task duration on gait symmetry. *Conditions differed based on the duration of the cognitive task (Intermittent in gray: 8 minutes, Complete in black and white lines: 14 minutes). Data are presented as mean values and standard error.* ***A) Magnitude of DSS symmetry****. A value of 0 represents baseline symmetry during tied belt walking.* ***B) Variability of Dual Support Symmetry****. A value of 0 represents baseline variability during tied belt walking.* ***C) Rate of Symmetry Adaptation and De-Adaptation.***

4.5 Discussion

Our findings suggest that dual tasking placement, rather than duration, within the split belt adaptation paradigm affected allocation of attention. An auditory cognitive task presented simultaneous to the onset of split belts reduced participants' initial cognitive task accuracy. Because gait symmetry was unaffected by the cognitive task during split belt adaptation, this

suggests a change attention allocation and task prioritization during the initial portion of adaptation.

Task prioritization affected by dual task in early adaptation

We observed reduced cognitive task accuracy during the initial phase of altering temporal gait symmetry to the split belt treadmill. When a cognitive task does indeed overlap with cognitive resources that are required for gait control, it is hypothesized that a reduction in cognitive performance and/or a decrement to gait performance would be present (Al-Yahya, Dawes et al. 2011). Performance of the auditory n-back task used here is hypothesized to involve the prefrontal cortex (working memory, Owen, McMillan et al. 2005), the posterior parietal cortex (short term memory storage, Smith and Jonides, 1998), and the pre-motor and supplementary motor areas (d'Esposito, Aguirre et al. 1998, Smith and Jonides 1998, Ravizza, Delgado et al. 2004), all areas which are highly involved in coordination of more complex walking tasks (Fukuyama, Ouchi et al. 1997, Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008, la Fougere, Zwergal et al. 2010, Gwin, Gramann et al. 2011, Takakusaki 2013). Therefore, as was expected in Experiment 1, participants who also experienced the initial split belt exposure were unable to maintain performance of the cognitive task at the same accuracy level as baseline. Instead of causing further gait perturbation, participants considerably decreased their accuracy. Given that this reduced accuracy occurred during a more rapid adjustment phase of adaptation, we hypothesize that gait performance was prioritized, drawing active attention away from cognitive resources normally available for the cognitive task

Immediate gait cycle adjustments to the onset split belts, the period with the greatest effect on the cognitive task, are typically focused on step length and stance phase duration (Reisman, Block et al. 2005, Lam, Anderschitz et al. 2006, Morton and Bastian 2006, Choi, Vining et al.

2009, Reisman, Bastian et al. 2010). Our results support the hypothesis that the nervous system controls the initial step-to-step corrections to the split belt treadmill differently from the actual locomotor adaptation process (Roemmich, Long et al. 2016). As such, while the initial accuracy to the cognitive task was reduced, it was unaltered once adaptation to split belts had occurred. Once the initial gait pattern changes to split belts had occurred and the adaptation process was underway, participants could once again allocate more attention to the cognitive task.

Young Adults easily adjust to a split belt adaptation with dual task

Healthy, young adults have the inherent capability and flexibility to not only adapt to split belt walking, but also attend to and respond to a continuous cognitive dual task. Previous literature has found, similar to our results, that young adults prioritize the motor task over the cognitive task in a dual task scenario (Malone and Bastian 2010, Sawers, Kelly et al. 2013, Vervoort, den Otter et al. 2019). In split belt adaptation, this has manifested as a slowed reaction time without change to whole body sagittal plane movement variability (Sawers, Kelly et al. 2013), a reduced response accuracy without change to magnitude of gait asymmetry (Vervoort, den Otter et al. 2019) or no change to adaptation of temporal gait phasing [11]. In contrast, McFadyen and colleagues found young adults prioritized cognitive over motor performance with an increase in dual support phase without a change in response time (McFadyen, Hegeman et al. 2009) and Malone and Bastian found a slowed rate of adaptation and de-adaptation of spatial gait symmetry without a change in the magnitude of step length asymmetry (Malone and Bastian 2010). Previous works have either administered the dual task throughout split belt walking (McFadyen, Hegeman et al. 2009), throughout split belt adaptation (Malone and Bastian 2010, Sawers, Kelly et al. 2013) or at the beginning and ending of the split belt Adaptation phase (Vervoort, den Otter et al. 2019). Interestingly, while we also saw that there were alterations to attention allocation initially when

both split belts and the dual task are administered simultaneously, our results indicate that dual task placement and duration during Adaptation do not affect the Post-Adaptation phase. Young adults further utilized their flexibility in locomotor control and were equally affected whether the dual task occurred throughout the Adaptation process or in intermittent bouts. If the dual task paradigm seeks to ensure participants are actively attending to another task while also completing the adaptation process, our results suggest that the dual task should likely be administered simultaneous to the onset of split belts but does not necessarily need to be maintained throughout the Adaptation period. In this way, healthy young adults can be challenged with a more complex or demanding cognitive task that incorporates breaks so as not to reach mental fatigue that would impede the locomotor adaptation process.

Study limitations

The findings of this study are not without limitations. Indeed, the walking speed used by our participants is slower than expected of a young, healthy group and could make direct comparison with previous studies more difficult. We believe participants may have chosen a slower walking speed as they were unfamiliar with the constraints of split belt walking. We believe using a preferred speed for each participant likely limited the amount of variability in the response to the dual task as the perceived effort for walking was similar across participants. Finally, it has been shown that secondary tasks involving internal interfering factors, such as mental tracking, disturb gait more than externally driven secondary tasks, such as an auditory cue-driven response like the one used in the current protocol that may have reduced the ability of the cognitive task to affect gait (Li, Krampe et al. 2005).

4.6 Conclusion

Our results suggest that while dual task performance is affected at split belt onset, dual task placement and duration do not affect temporal gait symmetry during split belt adaptation. Since dual task performance was reduced when both the start of the dual task and the start of split belts occurred simultaneously, we believe this to be an interference period of split belt adaptation. Given healthy young adults inherent flexibility to adapt gait to quite complex environments, these results support future work exploring the use of dual task in a rehabilitation setting with more complicated motor-cognitive dual task paradigms that would require intermittent breaks to avoid fatigue possibly affecting split belt adaptation.

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.PREFACE: Chapter 5

From the systematic review of the cerebral influence on split belt treadmill walking (Chapter 3), a strong influence of cortical regions in the adjustment phase of split belts was not hypothesized, yet in the previous study, this phase where the n-back task had the strongest influence of the n-back task. This interference suggests that cognitive resource overlap occurred between tasks and as such there were limited resources to attend to both tasks simultaneously. These results indicate two main conclusions that can be explored further. First, that the early adjustment phase of the adaptation period is not only reliant proprioceptive feedback informing spinal circuits. Secondly, we require more precise measurements of brain activation while walking to make more specific hypotheses of the role of supraspinal influence on this process.

In this next chapter, we were the first to quantify brain regions activated during a specific phase of split-belt walking using positron emission tomography (PET) imaging using an 18-fluorine- fluorodeoxyglucose (FDG) tracer. This imaging technique provides a measurement of brain metabolism during tracer uptake which occurred during split belt walking. We designed a protocol where participants recreated the initial adjustment period to asymmetric split belts, where cognitive influence was the strongest during dual-tasking, over the entire 30-minute uptake period. Brain metabolism was then compared to typical treadmill walking to assess for brain areas where a change in metabolism (increase or decrease) occurred to determine areas which change in activation. This chapter provides the first ever direct evidence of brain regions that change in activation when continuous step-by-step adjustments to the gait cycle are required.

Chapter 5: Adjusting gait step-by-step: Brain activation during split belt treadmill walking.

THESIS STUDY 3

Authors: Dorelle C. Hinton[1,2], Alexander Thiel[3,4], Jean-Paul Soucy[3], Laurent Bouyer[5,6], Caroline Paquette[1,2*]

Affiliations:

[1] Department of Kinesiology and Physical Education, McGill University, Montreal, Canada, H3A 2T5

[2] Centre for Interdisciplinary Research in Rehabilitation of Montreal (CRIR), Montreal, Canada, H3S 1M9

[3] Department of Neurology and Neurosurgery, McGill University, Montreal, Canada, H3A 2T5

[4] Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada, H3T 1E2

[5] Centre for Interdisciplinary Research in Rehabilitation and Social Integration (CIRRIS), Quebec, Canada, G1M 2S8

[6] Department of Rehabilitation, Faculty of Medicine, Université Laval, Quebec, Canada, G1V 0A6

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5.1 Abstract

When walking on a split belt treadmill, where each leg is driven at a different speed, a temporary change is made to the typical steady-state walking pattern. The exact ways in which the brain controls these temporary changes to walking are still unknown. Ten young adults (23±3y) walked on a split belt treadmill for 30 minutes on 2 separate occasions: tied-belt control with both belts at comfortable walking speed, and continuous adjustment where speed ratio between belts changed every 15 seconds. ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) imaging measured whole brain glucose metabolism distribution, or activation, during each treadmill walking condition. The continuous adjustment condition, compared to the tied-belt control, was associated with increased activity of supplementary motor areas (SMA), posterior parietal cortex (PPC), anterior cingulate cortex and anterior lateral cerebellum, and decreased activity of posterior cingulate and medial prefrontal cortex. In addition, peak activation of the PPC, SMA and PFC were correlated with cadence and temporal gait variability. We propose that a "fine-tuning" network for human locomotion exists which includes brain areas for sensorimotor integration, motor planning and goal directed attention. These findings suggest that distinct regions govern the inherent flexibility of the human locomotor plan to maintain a successful and adjustable walking pattern.

Key Words: Split belt Treadmill; ^{18}FDG PET Imaging; Locomotor Plan; Gait Alterations

Highlights:

- ^{18}FDG PET imaging measured brain activation during split belt treadmill walking.
- A "fine-tuning" network increased activity: SMA, PPC, ACC and Cerebellar Lobule VI.
- Aspects of the DMN (PCC, mPFC) decreased activity compared to typical walking.
- Unplanned locomotor plan updates require a widespread network of brain areas.

5.2 Introduction

The ability to quickly alter and fine-tune one's walking pattern requires asymmetrical adjustments in the patterns of step length, stance and swing between legs. In the laboratory, a split belt treadmill, with independently driven belts under each leg, can recreate the separate functions of each leg, similar to those occurring during rapid changes to the walking pattern. When belts suddenly start moving at different speeds without warning to the participant (split belts), a spontaneous reactive change must be made to the previous typical symmetrical steady-state walking pattern. However, with extended exposure to split belts, feedforward anticipatory gait control integrates ongoing sensorimotor information to update the motor plan, gradually allowing the central nervous system to create a context-specific locomotor program (Blanchette and Bouyer 2009, Reisman, Bastian et al. 2010). The ability to react to, and learn from, treadmill belts operating at different speeds highlights the nervous system's capacity to alter locomotion to perturbations from the environment. The exact neural correlates underlying these locomotor program adjustments are now only beginning to emerge.

Thus far, hypotheses of the neural control underlying reactive and anticipatory gait alterations to spilt-belt treadmill walking have been primarily based on studies of clinical populations. Within 5 steps of walking on split belts, gait cycle changes are present in subjects with damage to the midline cerebellum (Morton and Bastian 2006), cortical strokes (Reisman, Block et al. 2005), children who underwent hemispherectomy (Choi, Vining et al. 2009), Parkinson's disease (PD) patients (Dietz, Ziiistra et al. 1995) and even healthy infants prior to independent stepping (Yang, Lamont et al. 2005). While these reactive gait changes are not affected, feedforward anticipatory gait cycle changes necessary for adaptation are not fully

functioning in these populations, highlighting that cerebellar and supratentorial regions are required for learning a new locomotor pattern.

Anticipatory changes to the gait pattern occur as a result of a change in the motor plan from repeated exposure to the reactive gait changes with the goal of minimizing errors. la Fougere and colleagues (la Fougere, Zwergal et al. 2010) hypothesized that this error driven feedback would originate from the spinal cord, through cerebellum to brainstem and basal ganglia, and would create a functional loop with the supplementary motor areas (SMA). This would allow for alterations to the ongoing motor plan through the brainstem and for updates to environmental constraints (la Fougere, Zwergal et al. 2010). This functional network for planned walking modifications has been confirmed with other neuroimaging studies involving locomotion, suggesting that sensorimotor integration while walking would not only require cortical activation of SMA (Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008) but would also involve the posterior parietal cortex (PPC) (Lajoie, Andujar et al. 2010, Gwin, Gramann et al. 2011, Billington, Wilkie et al. 2013, Drew and Marigold 2015, Mitchell, Starrs et al. 2018, Wong and Lomber 2018) and primary motor and somatosensory areas (Fukuyama, Ouchi et al. 1997, Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008, Gwin, Gramann et al. 2011). Finally, lateral cerebellar areas have been implicated in goal directed, or anticipatory, foot placement changes (Ilg, Giese et al. 2008) and adaptation of the gait pattern to split belt walking (Morton and Bastian 2006) while midline cerebellar lesions indicate that this region has a role in the dynamic postural control required during typical straight walking (Bastian, Mink et al. 1998). In addition to further cortical activation, the healthy CNS also reduces activity in areas known to be part of the Default Mode Network (DMN) during task performance (Raichle, MacLeod et al. 2001). The DMN is active at rest and involved

in self-reference, memory and thought and deactivates when any motor tasks are performed including walking (Crockett, Hsu et al. 2017).

Previous studies suggest that anticipatory gait changes to split belt treadmill walking, but not reactive gait changes, are affected by cerebellar, cerebral or subcortical damage. This raises the question of whether it is possible that part of the underlying neural control for reactive gait changes is located within lower level structures such as the brain stem, vestibulo-spinal portions of the cerebellum and spinal cord? A more direct assessment of the healthy central nervous system responses to split belt walking, using functional neuroimaging for instance, could help provide a more detailed description of its control mechanism.

By means of the progressive accumulation of a radioactive glucose analog to map whole brain metabolism, neural activity imaged with ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) represents the brain's average activity over a 30 to 40-minute period. While this excludes ^{18}FDG PET for assessing events that take place over a short period of time, it does allow for the assessment of activities sustained over the entire uptake period, such as walking. Previous ^{18}FDG PET protocols have successfully generated hypothesizes of the brain areas involved when modulation of the gait pattern is required (la Fougere, Zwergal et al. 2010, Mitchell, Potvin-Desrochers et al. 2018, Mitchell, Starrs et al. 2018).

Using ^{18}FDG PET imaging, this project identified cerebral and cerebellar brain regions involved in the control of continuous gait modifications needed to successfully perform a split belt treadmill task in healthy young adults. We hypothesized that continuous gait modifications to changing inter-belt speed ratios on the split belt treadmill would increase levels of glucose metabolism (i.e. would recruit) areas involved in sensorimotor feedback integration and goal-

directed foot placement: the lateral portions of the cerebellum, supplementary motor areas and the posterior parietal cortex.

5.3 Methods

Subjects

Ten healthy, young adults (mean age=22±3 years, 5 male) with normal or corrected-to-normal vision and no history of diabetes, vestibular dysfunction, neurological, musculoskeletal or cardiopulmonary disorders participated in this study. All participants had experience walking on a regular treadmill but were naïve to walking on a split belt treadmill before their participation in this study. The experimental protocol was approved by the McGill Institutional Review Board and all participants provided written consent.

Equipment

For gait analysis, participants wore seven wireless inertial measurement units (IMUs; triaxial accelerometers, gyroscopes and magentometers; Opal^{TM}, APDM Inc., Portland, OR) on the sternum, forehead, sacrum, left and right wrist, and left and right lower shank. A split belt treadmill (Forcelink Dual Belted Treadmill on N-Mill Frame) consisting of two independently-operating belts separated by a 5cm gap and three safety bars (front, right and left sides) was used to induce a continuous speed change to the gait pattern (Supplementary Figure 5.1). While walking on the treadmill, participants wore a safety harness for fall protection that provided no mechanical support nor hindered movements. To compensate for differences in treadmill belt noise at different speeds, participants wore binaural over-ear headphones which played pure white noise while walking.

Laboratory familiarization visit

Participants first provided signed informed consent, completed questionnaires for Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) and completed the International Physical Activity Questionnaire (IPAQ, Craig et al 2003). IPAQ results confirmed that all participants reached, at a minimum, a moderate level of physical activity each week. Treadmill belt speeds were calculated from measurements of each participant's mean overground comfortable walking speed during 2 minutes along an 11m path with 180-degree turns at each end. Participants then walked on the treadmill with both belts at their typical walking speed (15 minutes) to familiarize to the treadmill and surroundings (Tied-Belt Treadmill Familiarization). Participants walked as they would on a day-to-day basis, with arms swinging naturally and gaze directed forwards. So that participants were aware of what speed changes may feel like and avoid any anxiety, two "splits", where one treadmill belt was slowed down (to 50% of their typical walking speed), were administered with ample warning (15 seconds).

FDG PET Imaging sessions

Participants completed two, 2.5-hour imaging visits to the laboratory and Brain Imaging Centre (Montreal Neurological Institute) (>48hours apart, mean 10±10days). On each testing day, all participants fasted overnight (>6 hours) to optimize cerebral ^{18}FDG uptake (Varrone, Asenbaum et al. 2009). Participants repeated the Tied-Belt Treadmill Familiarization prior to ^{18}FDG injection on each imaging session to ensure walking comfort and a steady-state gait pattern was achieved.

A mean 188MBq bolus (±11MBq) of [^{18}F]-FDG was then injected into the cubital vein. Within 2 minutes (mean=1.8±0.5 minutes) of injection, participants began the treadmill walking

trial. Upon uptake in the brain (heavily weighted towards the first 10 to 15 minutes after injection Huang, Phelps et al. 1980, Ginsberg, Chang et al. 1988), ^{18}FDG is retained within cells, where it can be imaged using Positron Emission Tomography (PET). On each imaging session, participants performed one of two treadmill conditions for 30 minutes, ensuring optimal tracer uptake, with the order of treadmill conditions being randomized between participants (tied-belt and continuous adjustments, see below). Tracer accumulation while walking represents mean whole brain glucose metabolism, during each trial. Both conditions were performed on the same treadmill with the same visual and auditory surroundings.

The tied-belt walking condition was used as the reference task to account for any metabolic activity associated with typical walking and dynamic postural control during walking. During tied-belt walking, participants walked with both treadmill belts driven at their typical walking speed for 30 minutes.

The continuous adjustment condition was used as the experimental task to isolate specific brain areas associated with ongoing changes to the gait pattern. During continuous adjustment, participants walked on the treadmill with the ratio of treadmill belt speeds changing every 15 seconds without warning to the participant for 30 minutes. Belt speeds at ratios of 100%, 50% or 33% of typical walking speed were randomly presented (See Figure 5.1) and were frequent enough that participants continuously adjusted their gait to the treadmill. The order of belt speed changes was the same for all participants and ensured that the number of speed reductions were evenly applied to both sides. To confirm the perception of these belt changes, participants completed a short survey about belt speeds and belt speed changes after the PET imaging was completed. Due to software error during collection, gait data was not collected for 2 participants during the continuous adjustment condition.

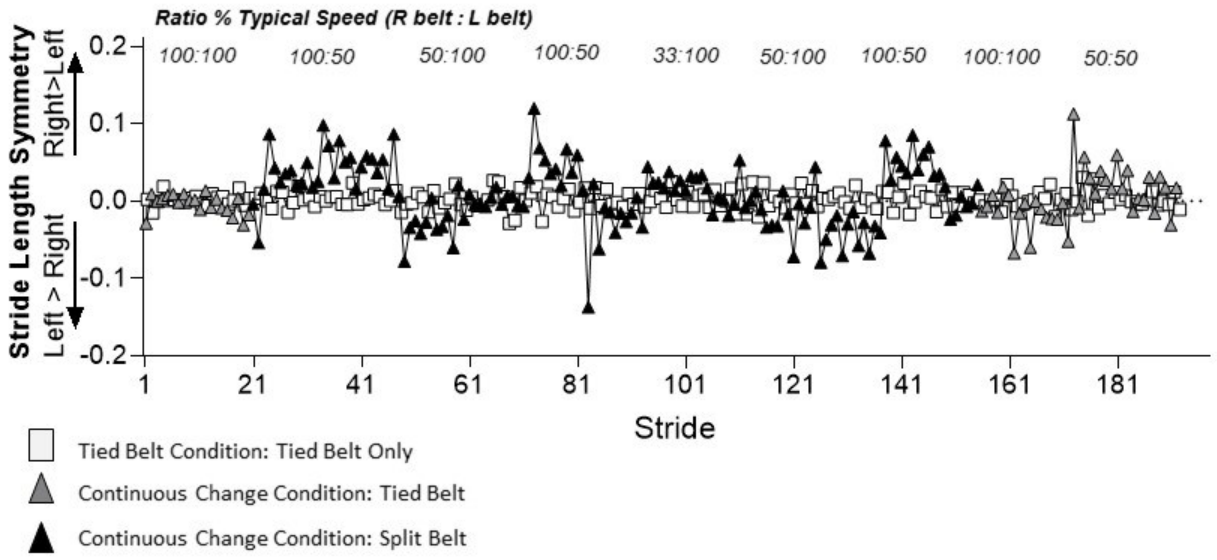


Figure 5.1: Example of Step-to-Step Symmetry for one participant. *While both belts remained at the participant's typical walking speed during tied-belt, the belt speed ratio was changed every 15 seconds during the continuous adjustment condition. The right and left belt speeds during the continuous adjustment condition are displayed as a percentage of typical speed, where 100% is equal to typical walking speed.*

PET and MRI Acquisition

PET image acquisition began within 50 minutes of injection (mean 48±7 minutes). This delay included the treadmill walking session (30 minutes), and a transition period for the participants to walk to the PET Imaging Centre at the Montreal Neurological Institute (MNI) (mean 5 ±1 minutes). Actual PET scan acquisition duration was 40 minutes followed by an additional 10 minutes of transmission scan time for attenuation correction. The combined walking time, transition and imaging time was within the 110-minute half-life of ^{18}F-FDG tracer (98±7 minutes).

Images were obtained with a High-Resolution Research Tomograph (HRRT) PET scanner (CTI/Siemens, Knoxville, Tennessee) with a spatial resolution of 2.3-3.4 mm at full width half maximum (Funck, Paquette et al. 2014). 3D sinograms were produced from the list-mode data acquired over 40 minutes and reformatted in a series of 8 successive 3D images of 5 minutes each. The use of 8 consecutive static images allowed for motion artefact correction. The 8 frames were then summed into a single 40-minute long frame.

T1-weighted anatomical images of the brain were acquired for co-registration with PET images on a 3 Tesla Siemens Trio Time Scanner (Siemens, Erlangen, Germany). A 3D magnetization rapid gradient echo was used (echo time: 2.98 ms; repetition time: 23 ms, flip angle=9°) resulting in a voxel size of 1x1x1mm obtained across the entire brain using an echoplanar imaging sequence (field of view = 240x256mm^2).

PET Image Preprocessing

All PET images were processed and compared using Statistical Parametric Mapping 12 (SPM12, Welcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK) running within MATLAB 2014b (MathWorks, Natick, Massachusetts, USA). Each condition's images (continuous adjustment or tied-belt) were linearly co-registered to the participant's native T1-weighted MR anatomical image. That MR study was co-registered and spatially normalized to the Montreal Neurological Institute template ICBM 152 6th generation linear brain atlas (Mazziotta, Toga et al. 2001). The 12-parameter affine transformation (Friston, Ashburner et al. 1995) allowing for co-registration of the subject's MR study to the template was then applied to the PET images already co-registered to the subject's MR in its native space, bringing both PET images into the MNI template space in a spatially normalized format. Using a Gaussian filter (Full width half Maximum=8mm), spatially normalized PET images were blurred

to minimize noise. Radioactivity concentrations in [Bq/ml] were then normalized to the average radioactivity concentration in the white matter using a mask of the centrum semiovale in MNI space, generating white matter-normalized Standardized Uptake Value Ratios (SUVRs). This step was used to remove the effects of inter-subject non-test condition linked differences in radioactivity concentration prior to voxel-based statistics (la Fougere, Zwergal et al. 2010).

PET Image Statistical Analysis

Whole Brain: Regional SUVRs were assessed for changes in brain activity during continuous walking adjustment compared to the tied-belt condition. To determine which brain regions are involved in the continuous alteration of the gait pattern, a flexible factorial design in SPM12 was used with treadmill condition (tied-belt, continuous adjustment) as the independent variable. Whole-brain group contrasts identified voxels of significant peak increase or decrease in glucose metabolism ($p<0.005$, uncorrected; Tard, Delval et al. 2015) and clusters of significant increase or decrease in glucose metabolism ($p<0.05$, FDR correction, minimum 30 contiguous voxels). Participants' peak z-scores from each cluster were extracted for regression analysis. All stereotactic coordinates refer to the MNI coordinate system.

Region of Interest: Following whole brain analyses, a secondary hypothesis emerged for the deactivation of the DMN. To test whether clusters of deactivation were identified within the known DMN, a single mask of 10mm spheres located at the DMN coordinates outlined by Andrews-Hanna et al (2010) was created and a whole-brain group contrast was repeated specifically within this mask (Supplementary Figure 5.2).

Gait Analysis

The spatiotemporal gait outcomes analyzed were obtained directly from the Mobility Lab^{TM} algorithms of the iWalk plugin for each gait cycle: 1) Cadence (steps per minute); 2) Stride Length (meters from heel contact to heel contact of the same leg) and 3) Proportion of the gait cycle spent in dual support. A relative measure of dual support was calculated based on which leg was approaching terminal stance: for instance left leg dual support occurred from right-foot heel contact to left-foot toe-off (Reisman, Block et al. 2005). Dual support for each leg was then expressed as a proportion of the gait cycle (% GCT).

Gait symmetry was assessed as the difference in performance in terms of stride length and dual support between each leg, presented as a ratio of the combined performance of both legs for that gait cycle; Step Symmetry = (Right Leg–Left Leg) / (Right Leg+Left Leg). A symmetry value of 0 indicates both legs performed at exactly the same level (Malone and Bastian 2010). To account for any inherent bias in each participant's gait symmetry, a mean symmetry was calculated from the first minute of tied-belt walking of each testing day and removed from all data points in the gait trial post-injection.

Learning (i.e. adaptation to split belts) did not occur during the continuous adjustment trial (stride length symmetry- 1st minute: 0.05+/-0.03; 15th minute: 0.05+/-0.02; 29th minute: 0.04+/-0.02 $p>0.05$; dual support symmetry- 1st minute: 0.11+/-0.04; 15th minute: 0.10+/-0.02; 29th minute: 0.11+/-0.04 $p>0.05$) so each participant's mean and standard deviation (SD) of stride length symmetry and dual support symmetry were calculated across the entire 30-minute trial to compare treadmill conditions. To further describe global stride-to-stride variability of symmetry measures, the proportion of steps (%total) each participant took beyond 2 SD of the tied-belt mean was calculated for both the tied-belt walking and continuous adjustment trial. Finally, to assess

whether [^{18}F]-FDG uptake was altered by the frequency of stepping, the percentage change in cadence from the tied-belt to continuous adjustment trial was calculated for each participant.

Gait Statistical Analysis

To determine overall differences in gait symmetry between treadmill conditions, one-way repeated measures ANOVA's were used to detect an effect of treadmill type (tied-belt, continuous adjustment) for 1) mean; 2) SD; and 3) number of steps outside 2SD threshold of each outcome measurement (dual support and stride length symmetry) for a total of 6 separate one-way ANOVA. Statistical tests were completed in SPSS Version 22 and deemed significant at $p<0.05$.

To determine if a relationship existed between individual participant's FDG uptake and their gait pattern, bivariate Pearson's correlations were calculated between participants' peak Z score within clusters of increased and decreased FDG uptake (determined from group level analyses) and gait outcome variables (%change in cadence from tied-belt walking, %steps outside tied-belt walking threshold, SD of symmetry measures). A linear regression was calculated to model participants' peak Z score within each significant cluster based on gait outcomes with significant correlations, corrections for multiple regressions were not applied. The regressions were assessed in SPSS Version 22 and deemed significant at $p<0.05$.

5.4 Results

Gait modifications required for continuous adjustment condition

The continuous adjustment condition successfully increased stride-to-stride variability beyond typical walking and required participants to alter their gait pattern in response to belt speed changes (Figure 5.1). Mean stride length symmetry and dual support symmetry were similar

between conditions (Figure 5.2A, $p>0.05$), however stride-to-stride symmetry variability increased during the continuous adjustment condition compared to the tied-belt (Figure 5.2 B-C, $p<0.05$). Standard deviation of participants' mean gait symmetry across all gait cycles were significantly greater during the continuous adjustment trial (Figure 5.2B: stride length: $F(1,7)=254.989$, $p<0.001$, dual support: $F(1,7)=504.652$,$p<0.001$). Participants spent a significantly greater percentage of strides outside of 2 standard deviations of their typical tied-belt gait symmetry pattern during the continuous adjustment trial than during tied-belt walking (Figure 5.2C: stride length: $F(1,7)=20.975$, $p<0.001$; dual support: $F(1,7)=43.060$, $p<0.001$).

While all participants felt they walked as they typically do during the tied-belt condition (1.14+/-0.05m/s), 8 of 10 participants felt they were not able to use their typical walking pattern during the continuous adjustment condition. All participants perceived belt speed ratio changes during the continuous adjustment trial, with 9 of 10 participants reporting that they thought these changes occurred every 30 seconds or less. Six of 10 participants reported they believed they could predict when the next belt speed change would occur, but not which leg would change.

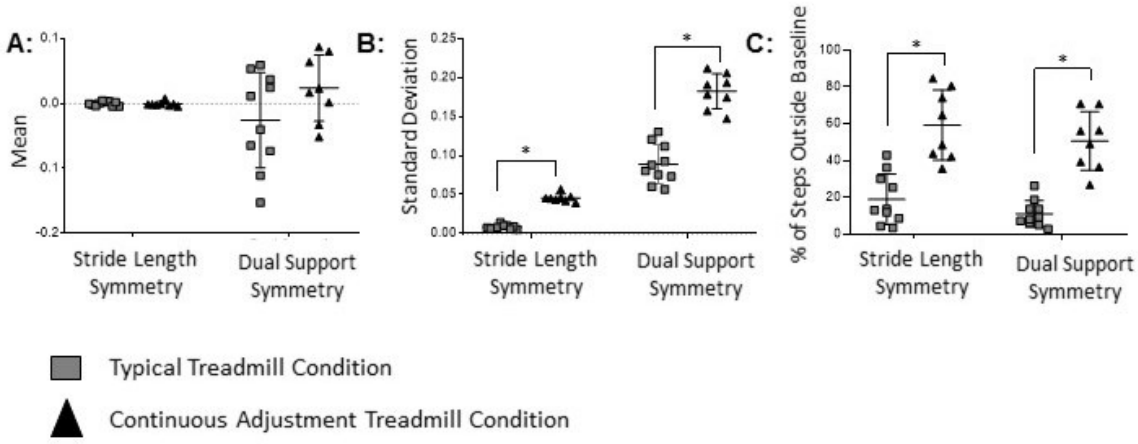


Figure 5.2: Walking performance. *Individual data points represent each participant. The group mean ± 1SE is represented with a solid line.* ***A)*** *Mean gait symmetry was not different between conditions (p>0.05).* ***B)*** *Gait symmetry standard deviation was greater during continuous adjustment (p<0.05).* ***C)*** *Participants had a significantly greater proportion of steps beyond 2 standard deviations of tied-belt mean during the continuous adjustment trial (p<0.05).*

Changes of brain metabolism regional distribution during continuous gait adjustments on the split belt treadmill.

During continuous gait pattern adjustments, in contrast with tied-belt treadmill walking, significant clusters of increased metabolism ($p<0.05$ FDR corrected, Figure 5.3, Supplementary Table 5.1) were found in the right PPC (Brodmann Area (BA) 5,7), right anterior cingulate gyrus (ACC, BA24), bilateral SMA (BA6) and left lateral cerebellum (lobules VI,VIII). Significant peaks of increased glucose uptake were also noted in the right insula, right inferior parietal lobe, the right precentral gyrus, the right thalamus and bilateral cerebellum ($p<0.005$, uncorrected).

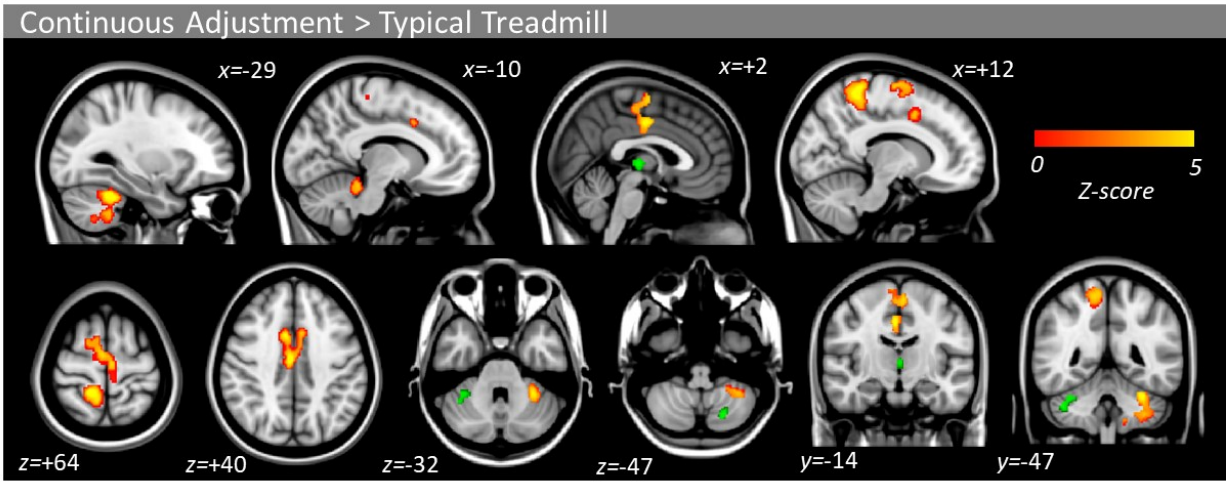


Figure 5.3: Activation maps for continuous adjustment of gait. *Compared to tied-belt walking, the continuous adjustment trial significantly increased glucose uptake in a cluster (FDR corrected $p<0.05$) in the left posterior parietal cortex, left anterior cingulate cortex, bilateral supplementary motor areas and right anterior cerebellum (Lobule VI, VIII). Significant increases in peak glucose uptake ($p<0.005$ uncorrected) are shown with green.*

A significant decrease in peak metabolism during continuous adjustments (compared to tied-belt walking) was found in the left posterior cingulate cortex (BA23, 31) ($p<0.005$ uncorrected, Figure 5.4, Supplementary Table 5.2). There was also evidence of a significant decrease in peak glucose metabolism in the left medial pre-frontal cortex (PFC), right ACC, left precuneus, right frontal gyrus and left superior temporal gyrus. To further explore and confirm these deactivations, specific region of interest analyses within areas known to be part of the DMN were performed. These secondary analyses further supported that the peak of activity decrease of the left posterior cingulate and inferior parietal cortex were both within the DMN, a known functional connectivity network (See Supplementary Table 5.3, Supplementary Figure 5.2, Andrew-Hanna, Reidler et al. 2010).

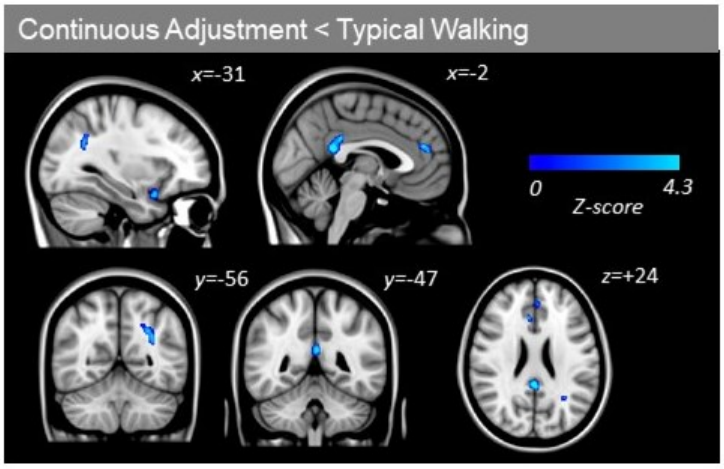


Figure 5.4: Deactivation maps for continuous adjustment of gait. *Compared tied-belt treadmill walking, the continuous gait adjustment trial significantly decreased peak glucose uptake ($p<0.005$ uncorrected) in a in the left posterior cingulate gyrus and left medial prefrontal cortex. Z-scores depicted are $p<0.005$ uncorrected.*

Associations between gait performance and neural correlates of continuous adjustments

A significant decrease in cadence from tied-belt cadence (a value of 0) was associated with a further increase of the PPC cluster. Compared to tied-belt walking, participants' increase in peak Z score within the cluster of right PPC activation during continuous adjustment was associated with a decrease in change in cadence (Z score=-6.445x%change cadence+2.362; $F(1,6)=16.15$, $p=0.007$, $R^2=0.7291$, Figure 5.5A).

A greater SMA cluster activation was associated with greater dual support symmetry variability. Compared to tied-belt walking, participant's increase in peak Z score within the cluster of the left SMA was associated with an increase in dual support symmetry SD (Z score=89.4 x dual support symmetry standard deviation–1.791, $p=0.0419$, $R^2=0.5256$, Figure 5.5B).

Finally, participants who had the greatest peak deactivation of the PFC cluster showed the lowest proportion of steps with a stride length symmetry outside of the tied-belt treadmill walking threshold. Compared to tied-belt walking, increases in the percentage of steps outside of 2 standard

deviation of the tied-belt mean were associated with decreased peak Z score within the left medial PFC (Z score=-0.03579 x %change+5.295; F(1,6)=7.154, p=0.0368, R^2=0.5439; Figure 5.5C).

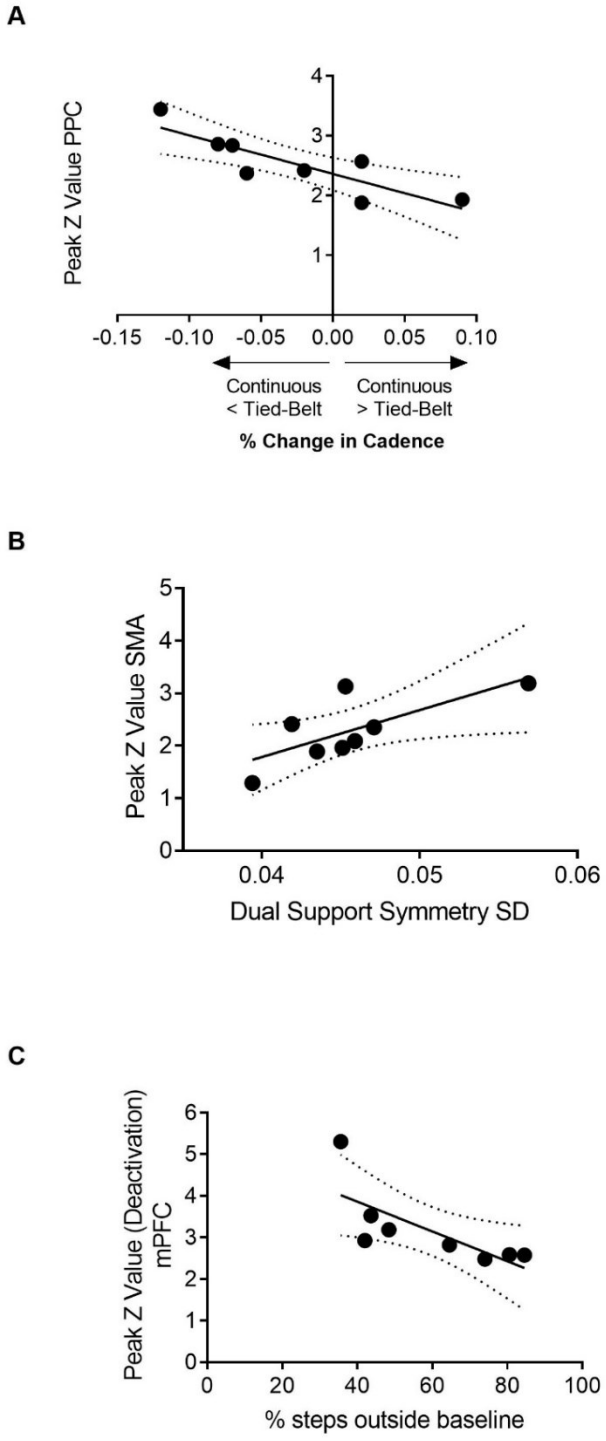


Figure 5.5. *Correlation between activated regions and gait parameters.* ***A:*** *A decrease in participants' cadence from the tied-belt to continuous adjustment trial was significantly related to an increase in peak activity (Z score) of the PPC cluster (p<0.05). Participants who increased cadence from the tied-belt to continuous adjustment trial, had a significant decrease in peak activity (Z score) of the PPC cluster (p<0.05).* ***B:*** *An increase in participants' dual support symmetry variability (continuous adjustment trial) was significantly related to an increase in peak activity (Z score) in the SMA cluster (p<0.05).* ***C:*** *A decrease in participants' percentage of steps outside of the tied-belt threshold (mean+/-2SD), that is lower variability, was related to a decrease in peak activity (Z score) in the PFC cluster (p<0.05).* ***Dotted*** *lines indicate a 95% confidence interval.*

5.5 Discussion

Our results indicate that when modifications to the gait pattern are required in response to unpredictable environmental perturbations, a distributed network across the entire brain is recruited (See Figure 5.6): there is increased activity of SMA, PPC, anterior cingulate cortex and anterior lateral cerebellum, and decreased activity of posterior cingulate and medial prefrontal cortex. In addition, peak activation of the PPC, SMA and PFC were correlated with cadence and temporal gait variability. Expanding on the network proposed by la Fougere and colleagues (la Fougere, Zwergal et al. 2010) we propose that error-driven sensorimotor feedback from lateral cerebellar lobule VI is relayed to cortical regions responsible for sensorimotor integration (PPC), motor planning (SMA) and goal directed attention (ACC) to inform any required changes to the motor program from the primary motor cortex. Activity from medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) decreases relative to typical walking, likely as an active release to direct cortical resource flow to motor planning regions. This proposed "fine-tuning" pathway for locomotion depicts changes in activity relative to typical, steady-state, treadmill walking.

Lateral cerebellum relays error-driven movement feedback to update locomotor plan

Our results provide direct evidence of what a variety of split belt adaptation protocols have previously hypothesized: the important role of the cerebellum in adjusting gait to asymmetrical belt speeds (Bastian 2006, Morton and Bastian 2006, Malone and Bastian 2010). As expected, participants increased recruitment of lateral cerebellar areas, specifically Lobules VI and VIII outside of the cerebellar vermis, during unpredictable step-to-step gait pattern changes. The cerebellum is a major hub of confluent information from both the spinal cord for sensory feedback and cortical regions for feedforward control (Takakusaki 2013). Lobule VI receives input from and projects output to the primary motor cortex via the pontine and dentate nuclei and thalamus

and thus has been hypothesized to be primarily a sensorimotor region of the cerebellum (Glickstein, May III et al. 1985, Kelly and Strick 2003) and a movement error sensor (Kitazawa, Kimura et al. 1998, Imamizu, Miyauchi et al. 2000, Diedrichsen, Hashambhoy et al. 2005).

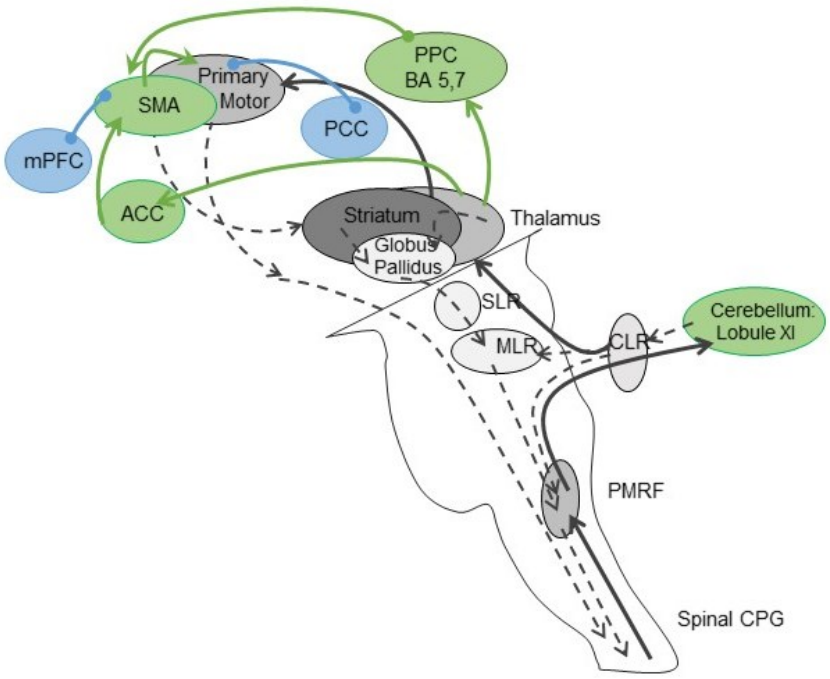


Figure 5.6: ***The "fine-tuning" network of locomotion.*** *Step-to-step gait pattern changes require increased activity (green) and decreased activity (blue) of cortical regions compared to typical walking (grey). This model elaborates on the "executive" and "planning" networks of locomotion proposed by la Fougere et al. (2010). SLR: subthalamic locomotor region; MLR: mesencephalic locomotor region; CLR: cerebellar locomotor region; PMRF: pontine and medullary reticular formations; CPG: Central Pattern Generator.*

Increased activity in the cerebellum during gait modification aligns with the hypothesis of the cerebellum as an error driven and feedforward sensor (Bastian 2006). In the context of walking, this area is thought to be involved in motor learning and updating of the internal locomotor plan (Imamizu, Miyauchi et al. 2000). During locomotion, cerebellar climbing fibres increase their activity, coding for predicted error severity during the stance portion of the perturbed leg and the swing phase of the next step, and allowing for planning of the next foot placement (Yanagihara and Udo 1994). Finally, damage within the cerebellar hemispheres makes gait adaptation to split

belts (i.e. learning) impossible (Morton and Bastian 2006). Though our participants were never at a belt ratio long enough to show gait pattern adaptation, we believe that this lateral cerebellar activation is a result of an accumulation of 30 minutes of attempting to integrate ongoing changes to the locomotor plan.

Posterior parietal cortex activation for reactive gait adjustments.

While previous work has demonstrated a change in PPC activity during obstacle avoidance in cat locomotion, additional PPC activation has not previously been hypothesized during unpredictable human gait modification or adjustments to split belt treadmill walking. We suggest this activation would complement feedback from lateral cerebellum to inform updates to the locomotor plan. It is likely that the PPC activation during these gait adjustments reflects an increased associative workload needed to integrate visual and proprioceptive information with the ensuing movement of each leg. During direct electrophysiological recordings in the PPC of walking cats, BA 5 increased activity during obstacle avoidance with obstacles held in working memory (Lajoie, Andujar et al. 2010, Drew and Marigold 2015), obstacle avoidance with and without tactile feedback (Wong and Lomber 2018), and obstacle avoidance without visual information (Marigold and Drew 2011). Given that proprioceptive information from the feet would be especially important during treadmill walking, being one of the first sensory cues of a belt speed change, our results support the hypothesis that the PPC actively participates in integrating sensory information for specifying motor outputs for the upcoming step in the human CNS.

In humans, the PPC has also been suggested to generate a body schema that would be responsible for integrating limb movement, and their movements relative to the body, with information about the environment (Takakusaki 2013). During continuous belt speed changes, a body schema representation would likely incorporate sensorimotor feedback from each leg

separately based on both placement and timing into modifications of the motor plan for upcoming steps. In addition, activations of the PPC together with the ACC and SMA, are thought to be involved in visuo-motor integration and error monitoring (Gwin, Gramann et al. 2011). The use of the PPC for sensory integration, body schema error monitoring and holding environmental constraints in working memory would allow the PPC to assist the SMA and primary motor cortices in selecting subsequent locomotor plan updates (Drew and Marigold 2015). Indeed, by integrating real-time signals of sensory feedback to the body schema, information can then be passed on the SMA for motor program updates and planning for upcoming steps (Lajoie, Andujar et al. 2010).

The Supplementary Motor Area and Anterior Cingulate Cortex participate in updating the locomotor plan.

In conjunction with PPC activity, our results suggest that SMA and ACC activations are required for fine-tuning the stepping pattern in response to a change to the belt speed ratio. In fact, participants with the greatest between-step changes to gait phasing also had the greatest overall increase in SMA activity, supporting the role of SMA for fine-tuning gait modifications. Brain activation studies during gait have pointed to the SMA's role in motor planning, motor programming for voluntary movements and maintaining rhythmic stepping (Fukuyama, Ouchi et al. 1997, Harada, Miyai et al. 2009). SMA activity increased just prior to both routine and precision stepping, without further change during the actual execution of these tasks (Koenraadt, Roelofsen et al. 2014) pointing to a role for the SMA in movement initiation planning which became significantly more complex in our continuous gait change protocol.

It is well understood that the ACC increases its activity for focused attention and cognitive processing selection (Pardo, Pardo et al. 1990). In addition, the ACC was shown to be linked to foot placement monitoring and ongoing error correction (Bush, Luu et al. 2000, Gwin, Gramann

et al. 2011) as well as to be active just prior to a goal directed movement (Cole and Schneider 2007). In conjunction with PPC and SMA, ACC activity would allow the nervous system to implement updates to stance and swing as appropriate to the environment (i.e. the belt speed under each foot in our protocol). As participants do not know the exact moment of the belt speed changes, one possible explanation to the increase in SMA and ACC activity would be that those structures are primarily required for online adjustment and anticipation of a possible fine tuning of the gait pattern in response to a belt speed change.

Continuous gait adjustments further reduced activation of the default mode network

Our findings re-emphasize the ability of the healthy CNS to reduce DMN activity during motor task performance. Involved in self-reference, memory and thought, the DMN is active at rest (Raichle, MacLeod et al. 2001) and deactivates to some extent with any movement, including walking (Crockett, Hsu et al. 2017). More specifically, deactivation of the posterior cingulate was also related to feelings of undistracted attention or letting go of directed task-related attention (Garrison, Santoyo et al. 2013) and could act as a potential cognitive release to allow motor and motor planning areas to alter the ongoing locomotor plan. The medial PFC is typically discussed as a regulator of higher cognitive input and/or executive functions (Koechlin and Hyafil 2007) and typically increases its activity with new experience. However with exploration of a repeated task and using feedback to reduce error, this area has been shown to decrease its activity (Koechlin, Danek et al. 2002). In fact, participants who reduced activity the most within the medial PFC cluster during continuous adjustments were least variable in their stride-to-stride placement. Given the participants' high step-to-step variability imposed by the split belt task, they were less able to predict belt speed changes and instead had to use on-the-fly sensory information as it was processed to implement gait pattern changes. In doing so, the less the participants used higher

order cognitive resources to attend to the ongoing treadmill changes, the more control their neural system was able to exert on a stride-by-stride basis. Within this hypothesis, activation of the PFC would likely only impede or slow down this sensory integration and ensuing step-to-step changes therefore is unnecessary or even counterproductive.

Study Limitations

While FDG-PET imaging provides excellent spatial resolution, its temporal resolution is limited to the entire uptake period and we cannot comment on specific gait cycle events or time points within the uptake period. As we chose to look at the neural activity associated with step-to-step gait adjustments, we selected tied-belt walking as our reference task, and we cannot comment on brain activity required for typical treadmill walking on its own.

5.6 Conclusion

We propose that a "fine-tuning" network for human locomotion exists which includes brain areas for sensorimotor integration, motor planning and goal directed attention. While some areas increase in activity relative to typical treadmill walking (cerebellum lobule VI, PPC, SMA, ACC), others act as a cognitive release and decrease in activity relative to typical treadmill walking (posterior cingulate gyrus, medial PFC). Ongoing and flexible changes to the walking pattern are made through error detection and visuo-motor and tactile sensory integration. Gait pattern changes are facilitated by a deactivation higher order cognitive control, liberating resources for motor planning and execution. These findings point to the inherent flexibility of the human locomotor plan to react and adjust to environmental changes, updating its activity as information arrives from

current motor activity in order to optimize performance during the upcoming step, maintaining a successful walking pattern.

Supplementary Table 5.1: Increased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking)

Whole Brain, voxel p<0.005 (uncorrected), cluster minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FDR Corr	P uncorr	Cluster size	t	Z	Q FDR-corr	P uncorr	X	Y	Z
R Precuneous / Postcentral Gyrus (Posterior Parietal Cortex)	5,7	0.007	0.001	419	6.8	4.72	0.044	0.000	16	-42	64
R Anterior Cingulate Gyrus / R/L Medial Precentral Gyrus (Supplementary Motor Area)	24	0.000	0.000	962	6.52	4.62	0.044	0.000	4	-12	40
	32				5.89	4.34	0.074	0.000	8	8	42
	6				4.89	3.85	0.214	0.000	-4	-18	62
R Insula / Inferior Parietal Lobule	13	0.196	0.039	133	5.69	4.25	0.084	0.000	46	-30	22
R Insula / Precentral Gyrus	44	0.324	0.139	63	5.33	4.07	0.130	0.000	46	2	8
R Thalamus		0.232	0.077	93	4.32	3.53	0.308	0.000	2	-18	2
	Cerebellum										
L Lobules VI, VIII		0.007	0.001	421	6.48	4.6	0.044	0.000	-30	-44	-30
					4.86	3.84	0.214	0.000	-34	-46	-46
					3.21	2.82	0.803	0.002	-20	-42	-50
L Lobules III, IV, V		0.230	0.066	102	3.99	3.33	0.308	0.000	-10	-38	-20
L Lobules VIIb, VIII		0.304	0.116	72	3.86	3.25	0.558	0.001	-20	-68	-46
R Lobules VI, Crus I		0.196	0.047	122	4.53	3.65	0.245	0.00	42	-44	-40
					3.6	3.08	0.636	0.001	34	-44	-30
					3.26	2.85	0.803	0.002	38	-52	-30

Supplementary Table 5.2: Decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking).

Whole Brain, p<0.005, minimum 30 voxels

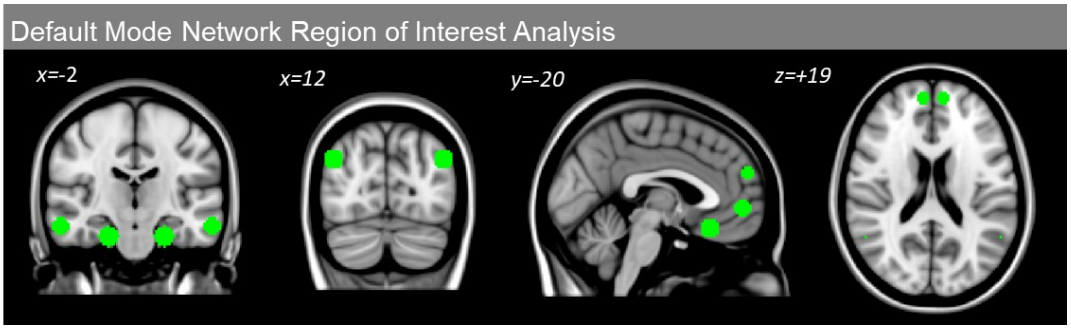
		Cluster				Peak					
Brain Region	BA	P FWE Corr	Q FDR Corr	P uncorr	Cluster size	t	z	P uncorr	X	Y	Z
Left Posterior Cingulate	31, 23	0.299	0.200	0.011	221	5.14	3.98	0.000	-4	-54	22
Left medial prefrontal cortex	10	0.994	0.575	0.151	59	4.28	3.51	0.000	-6	54	22
						4.01	3.35	0.000	-8	60	16
R Anterior Cingulate	32	1.000	0.866	0.292	31	3.68	3.14	0.001	6	36	28
L Precuneus / Inferior Parietal	39	0.952	0.575	0.09	85	3.65	3.12	0.001	-40	-70	32
						3.46	2.99	0.001	-30	-66	46
						3.35	2.91	0.002	-34	37	40
R Frontal Gyrus	11	0.984	0.575	0.123	69	3.63	3.11	0.001	40	38	-16
						3.10	2.74	0.003	38	48	-16
L Superior Temporal Gyrus	38	0.984	0.575	0.123	69	3.55	3.05	0.001	-40	14	-30
						3.16	2.78	0.003	-36	18	-16
						2.98	2.65	0.004	-36	14	-10

Supplementary Table 5.3: Decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking).

Masked to Default Mode Network, 10mm spheres, (Andrews-Hanna, Reidler et al. 2010), p<0.005, minimum 30 voxels

		Cluster				Peak					
Brain Region	BA	P FWE Corr	Q FDR Corr	P uncorr	Cluster size	t	z	P uncorr	X	Y	Z
Left Posterior Cingulate	31, 23	0.117	0.222	0.053	114	5.14	3.98	0.000	-4	-54	22
L Precuneus / Inferior Parietal	39	0.476	1.000	0.277	33	3.65	3.12	0.001	-40	-70	32

Supplementary Figure 5.1: Split belt treadmill walking. *Independently driven belts running at different speeds.*



Supplementary Figure 5.2: Default Mode Network (DMN) Region of Interest Analysis. *A single mask of 10mm spheres located at the DMN coordinates outlined by Andrews-Hanna et al (2010).*

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PREFACE: Chapter 6

Parkinson's disease (PD) is a pathology of the basal ganglia, and a nervous system affected by PD has a reduced ability to produce smooth, coordinated movements, making complex walking scenarios much more difficult. One of the key symptoms of reduced movement control occurs during walking, where disease progression manifests as slower, shuffling gait. However, despite these disease-related changes to automaticity of locomotor control, the systematic review of split belt literature (Chapter 3) suggested that adults with PD can adapt their gait pattern to a split belt treadmill and that the basal ganglia had minimal impact on adjusting the gait cycle to the split belt treadmill. From the analysis of healthy, young adults in Chapter 5, a *Fine-Tuning Network* was proposed that aids in the control of unplanned step-to-step gait pattern adjustments in a healthy young nervous system. While a change in activation of the basal ganglia was not observed, a network of sensory integration and motor planning areas were involved in the fine tuning of the gait pattern to accommodate and adjust to walking with belts at different speeds and continuously changing speed ratio. These planning areas receive direct input from the basal ganglia and could therefore be indirectly affected by PD.

The next study set out to identify the neural correlates of gait adjustments to the split belt treadmill in adults with PD. Using the same neuroimaging analysis as Chapter 5, the network of brain areas activated to adjust the gait cycle to walk on the split belt treadmill will be identified in healthy older adults and adults with PD and comparisons to typical treadmill walking will be made to identify areas specific to complex locomotion. Finally, the proposed *Fine-Tuning Network* from Chapter 5 will be expanded to include changes that occur with PD.

Chapter 6: Parkinson's disease affects neural activation during continuous gait alterations to the split belt treadmill: An [18F] FDG PET Study.

THESIS STUDY 4

Authors: Dorelle C. Hinton[1,2], Alexander Thiel[3,4], Jean-Paul Soucy[3], Caroline Paquette[1,2*]

Affiliations:

[1] Department of Kinesiology and Physical Education, McGill University, Montreal, Canada, H3A 2T5

[2] Centre for Interdisciplinary Research in Rehabilitation of Montreal (CRIR), Montreal, Canada, H3S 1M9

[3] Department of Neurology and Neurosurgery, McGill University, Montreal, Canada, H3A 2T5

[4] Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada, H3T 1E2

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6.1 Abstract:

Background: Split belt (SB) treadmill walking, where each leg is driven at a different speed, highlights the nervous system's ability to quickly alter both step length and stride phasing. Interestingly, adults with Parkinson's Disease (PD), who experience reduced automaticity of locomotor control and difficulty in step-to-step changes, are also capable of adapting their gait pattern to a SB treadmill. The neural correlates underlying these rapid gait pattern changes are emerging. Here, we compared cortical and subcortical activity during SB treadmill walking with continuous belt speed changes to typical treadmill walking to determine how brain areas activated by continuous asymmetrical gait speed changes are altered by PD.

Methods: Ten older adults and 10 adults with PD performed SB treadmill walking for 30 minutes on 2 separate occasions: 1) Control- both belts at comfortable walking speed, and 2) Continuous Change- speed ratio between belts changed every 30 seconds. A bolus injection of ^{18}F-fluorodeoxyglucose (FDG) tracer (a glucose analog) immediately prior to walking measured whole brain glucose metabolism, or activation, during each trial. Upon uptake in the brain (20 minutes), FDG is held within the cell, where it can be imaged using Positron Emission Tomography (PET) before its half life is complete (109 minutes). PET images of glucose metabolism from each condition were compared to assess for increases in metabolism when continuous gait pattern changes are required and to determine the effects of aging or PD.

Results: During continuous belt speed changes adults with PD increased supplementary and primary motor area, posterior parietal cortex, posterior cingulate and right and left cerebellum (lobule I-IV) compared to typical treadmill walking. In addition, adults with PD had a cluster of significantly greater activation within the premotor, supplementary and primary motor areas compared to healthy older adults.

Conclusion: Participants with PD required a broader neural network to accommodate continuous asymmetric treadmill belt speed changes. Compared to typical treadmill walking, all participants used proper activation of motor planning and sensory integration areas, task directed attention and updating an internal locomotor plan. The presence of PD required even further activation from primary motor and sensorimotor integration areas. This widespread use of cortical and subcortical neural networks may help to explain why more complex walking tasks, such as dual tasking or turning, show detriments with aging and progression of PD.

6.2 Introduction

In a typical day-to-day scenario, we require the use of a varied gait pattern. Approximately 35-45% of our total daily steps are in the process of making a turn where time spent in stance and swing, step lengths of each leg and gait speed will all be different than typically used during straight walking (Glaister, Bernatz et al. 2007). While most of these turns will be planned a few steps in advance, for instance as we walk from a room and into a hallway, sometimes we must make last second changes to our walking pattern to avoid an unseen obstacle or a sudden change in direction. A healthy nervous system allows young adults to complete these types of changes in a wide variety of surroundings, including a crowded street or hallway or while walking and talking with a friend. However, a nervous system affected by Parkinson's disease (PD) has a reduced ability to produce smooth, coordinated movements, making complex walking scenarios such as turning much more difficult (Plotnik and Hausdorff 2008).

PD is a pathology of the basal ganglia, where the typical inhibitory pathways of the basal ganglia are overexcited, leading to a reduction of the excitatory signals sent via the thalamus to

the cortex (Alexander, Crutcher et al. 1990, Buhmann, Glauche et al. 2003). This causes a reduced ability to produce smooth, coordinated movements, especially during sequential (Benecke, Rothwell et al. 1987) or complex movement control (Berardelli, Dick et al. 1986). One of the key symptoms of reduced movement control occurs during walking, where disease progression manifests as slower, shuffling gait (Morris, Iansek et al. 1994). However, despite these disease-related changes to automaticity of locomotor control, adults with PD can adapt their gait pattern to a split belt treadmill. During split belt treadmill walking, where each leg is driven on a separate treadmill belt at a different speed, highlights the nervous system's ability to quickly alter both step length and stride phasing (Reisman, Block et al. 2005). Across a variety of paradigms, adults with PD adapt gait similarly to age-matched controls both in terms of gait variability and gait coordination (Seuthe, D'Cruz et al. 2019) and in both the ON and OFF Dopamine medication states (Nanhoe-Mahabier, Snijders et al. 2013, Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Mohammadi, Bruijn et al. 2015). However, at later stages of PD, whereby participants experience freezing of gait, gait adaptation and perception of the belt speed discrepancy become more difficult (Nanhoe-Mahabier, Snijders et al. 2013, Mohammadi, Bruijn et al. 2015, Bekkers, Hoogkamer et al. 2017).

Given the lack of difference between healthy older adults and adults with PD in altering their gait pattern to accommodate belts at different speeds, the role of the basal ganglia in altering the gait cycle could be questioned. Indeed, the neural correlates underlying these rapid gait pattern changes are developing. We recently asked young healthy participants to continuously adjust their gait pattern to a split belt treadmill and measured whole brain metabolism using a positron emission tomography (PET) image of ^{18}Fluorine- fluorodeoxyglucose (^{18}F-FDG) uptake over the course of thirty minutes of active walking (Hinton, Thiel et al. 2019). Compared to their whole

brain activity during typical treadmill walking, participants increased activity within a network of cortical areas deemed necessary for fine-tuning the walking pattern: motor planning (supplementary motor area) and sensory integration areas (posterior parietal cortex), task directed attention (anterior cingulate cortex) and updating an internal locomotor plan (anterior cerebellum) (Hinton, Thiel et al. 2019). Given the wide array of cortical areas implicated in this complex walking task, we are now interested to understand how a group of adults with PD would perform biomechanically on the split belt treadmill and if any compensatory cortical activations would be required.

Both the basal ganglia and cerebellum are activated for new learning of a movement, activation that is not simply due to the action being carried out (Jueptner, Frith et al. 1997, Jueptner, Stephan et al. 1997).The basal ganglia project to multiple cortical areas via the thalamus, many of which would be active during locomotion: primary motor, premotor, and supplementary motor areas, pre supplementary motor area, and cingulate. In addition, there is evidence of compensatory changes in cortical activation during movement in adults with PD that is not limited to diminished activation of the basal ganglia. For instance, joystick movements at rest saw impaired activation of putamen, anterior cingulate, SMA and dorsolateral prefrontal cortex (DLPFC) (Playford, Jenkins et al. 1992). Even in early stage PD, when motor impairments may be minimal and/or only unilateral, decreased activation in bilateral SMA and contralateral M1 to hand movements are observed and are reversed back to normal with dopamine medication (Buhmann, Glauche et al. 2003). During continuous steering of the walking pattern, adults with PD increased activity of the PPC and decreased activity in the DLPFC compared to typical straight walking with further changes occurring with disease severity (Mitchell, Potvin-Desrochers et al. 2019). However, these

the variety of cortical and subcortical studies of PD do not fully explain how adults with PD can walk on the split belt treadmill without further deficits to their gait pattern.

Here we set out to determine how PD affects cerebral and cerebellar metabolism during continuous adjustments of the gait cycle to belt speed changes on a split belt treadmill. Using 18F-FDG PET imaging, we compared areas of activation and de-activation during continuous gait adjustments in healthy older adults and adults with PD to establish how the network of brain areas utilized to adjust and re-adjust the gait cycle to the belt speed changes is altered with PD. It was expected that cerebral compensations would be required for adults with PD to appropriately adjust their gait pattern biomechanics to the split belt treadmill. We hypothesized that PD related decreases in activation of motor areas (SMA, M1, Premotor) would increase the reliance on cortical areas for sensory information and sensory integration. This would allow for a compensation in the decrease in dopamine production and allow for the production of the movement and movement changes required for the gait adjustments to occur. Based on our previous work in healthy young adults, we also expected the use of motor planning and sensory integration areas such as the SMA, PPC and lateral Cerebellum to accomplish these gait pattern adjustments properly.

6.3 Methods

Subjects

Ten adults with PD (mean age=64±5 years, 6 male) and ten age-matched healthy older adults (mean age=64±5 years, 5 male) with normal or corrected-to-normal vision and no history of diabetes, vestibular dysfunction, neurological, musculoskeletal or cardiopulmonary disorders

participated in this study (See Table 6.1). The experimental protocol was approved by the McGill Institutional Review Board and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

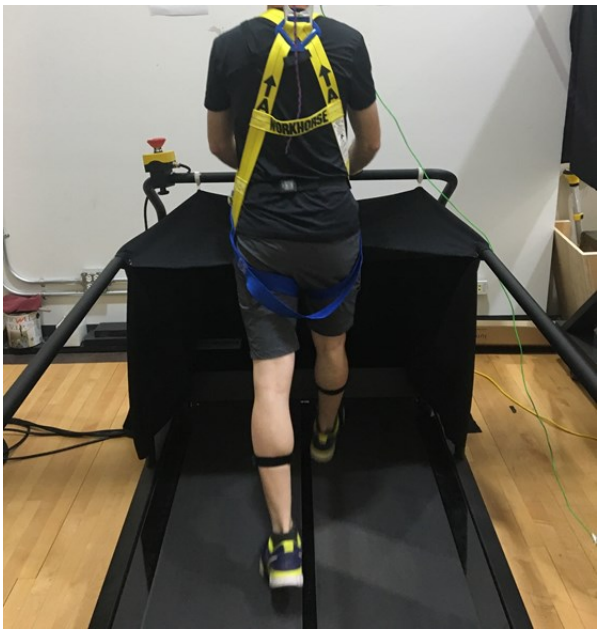
Table 6.1: Subject Characteristics

	Adults with PD	**Healthy Older Adults**
Sex (male/female)	6 / 4	5 / 5
Age (years)	65±5	66±4
Treadmill Walking Speed (m/s)	0.9±0.2	0.9±0.1
MoCA	26±2	27±2
Time since disease onset (years)	8±5	-
MDS-UPDRS-III – ON medication	35±9	-
MDS-UPDRS-III – OFF medication	32±5	-
Hoehn & Yahr scale	2.2±0.3	-

Equipment

For gait analysis, participants wore seven wireless inertial sensors (triaxial accelerometers, gyroscopes and magentometers; weight: 22 grams; Opal^{TM}, APDM Inc., Portland, OR) on the sternum, sacrum, left and right upper shank (medial to tibia), and the top of left and right shoes. Data continuously and wirelessly streamed to a computer with Mobility Lab^{TM} software (APDM Inc., Portland, OR). Participants walked on a split belt treadmill (Forcelink Dual Belted Treadmill on N-Mill Frame) consisting of two independently-operating belts separated by a 5cm gap and three safety bars (front, right and left sides). While walking on the treadmill, participants wore a safety harness for fall protection providing no mechanical support or hindering movement. No falls occurred during this study. To prevent visual feedback, a cloth treadmill "apron" prevented participants from seeing their feet or the treadmill belts (see Supplementary Figure 6.1). Finally,

participants wore binaural over-ear headphones playing pure white noise to mask treadmill belt noise at different speeds.



Supplementary Figure 6.1: Split belt treadmill setup. Participants were asked to walk with one foot on each treadmill belt and their hand resting on the front safety bar. A black "apron" prevents participants from observing the treadmill belts or their feet while walking.

Laboratory familiarization visit

All participants first completed a 1-2 hour visit where they provided signed informed consent, completed questionnaires for Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) as well as the Montreal Cognitive Assessment (Nasreddine, Phillips et al. 2005), the Waterloo footedness questionnaire (Elias, Bryden et al. 1998) and a general questionnaire about their overall health and activities of daily living. Participants with PD also completed Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) motor assessment to rate their disease severity and assess the leg most affected by PD-related symptoms.

While some participants had experience with treadmill walking, all were naïve to split belt treadmill walking. Because treadmill belt speeds were set to each participants' typical walking speed, overground comfortable walking speed was measured over a 2-minute trial along an 11m

path with 180-degree turns at each end. Turning behaviour (1 step prior to the turn, all steps during and 1 step out of the turn) was removed from the overground gait data and a mean steady-state walking speed, deemed their typical walking speed, was obtained from the middle minute for each participant.

Participants then walked on the treadmill with both belts at their typical walking speed for 15 minutes to allow for any gait adjustments to the treadmill and surroundings (*Tied-Belt Treadmill Familiarization*). Participants were asked to walk as they would on a day-to-day basis, with hands resting on the safety bar at the front of the treadmill and gaze directed forwards. So that participants were aware of what speed changes may feel like and avoid any anxiety during the imaging sessions, two "splits", where one treadmill belt was slowed down (to 50% of their Baseline Walking speed), were administered with ample warning during this first initial 15-minute treadmill session. Each split lasted for 15 seconds with the second split repeated on the other side.

FDG PET Imaging sessions

Participants completed two, 2.5-hour imaging visits to the laboratory and Brain Imaging Centre (Montreal Neurological Institute) no less than 48 hours apart to avoid inter-scan contamination (mean±SD: PD: 11±8 days, Control 5±2 days). Participants arrived at the laboratory after fasting for at least 12 hours to optimize cerebral [^{18}F]-fluorodeoxyglucose (FDG) uptake (Varrone, Asenbaum et al. 2009). Participants with PD were assessed in the OFF state of medication taking their last dose of L-DOPA medication 12 hours prior to arrival. Part III of the PD motor assessment was administered upon arrival. All participants repeated the *Tied-Belt Treadmill Familiarization* (with 2 "splits" as mentioned above) prior to [^{18}F]-FDG injection on each imaging session to ensure walking comfort and a steady-state gait pattern was achieved.

After the treadmill familiarization was complete, a bolus (PD: 5.3±0.2 mCi; Control: 5.2±0.3 mCi) of [^{18}F]-FDG tracer was injected into the cubital vein. Within 2 minutes (PD: 2.0±0.2 minutes; Control: 1.9±0.3 minutes) of injection, participants began the treadmill walking trial. Upon uptake in the brain (completed within ~30 minutes), FDG is trapped within cells, where it can be imaged using Positron Emission Tomography (PET). On each imaging session, participants performed one of two treadmill conditions for 30 minutes, thus meeting uptake time requirements, with the order of treadmill conditions randomized between participants (*tied-belt* and *continuous adjustments*, see below). Tracer accumulation while walking represents mean whole brain glucose metabolism, during each trial. Both conditions were performed on the same treadmill with the same visual and auditory surroundings.

The *tied-belt* walking condition was used as the reference task to account for any metabolic activity associated with typical walking and dynamic postural control during walking. During tied-belt walking, participants walked with both treadmill belts driven at the same speed as during the treadmill familiarization, for 30 minutes. No changes to treadmill belt speeds were administered.

The *continuous adjustment* condition was used as the experimental task to isolate specific brain areas associated with ongoing changes to the gait pattern. During continuous adjustment, participants walked on the treadmill with the ratio of treadmill belt speeds changing every 30 seconds without warning to the participant for 30 minutes. Belt speeds at ratios of 100%, 70% or 50% of typical walking speed were presented (See Figure 6.1 A and B for a sample of speed changes and corresponding gait symmetry changes). Belt ratio changes were frequent enough that participants were continuously adjusting their gait to the treadmill. Of the 30 minutes spent walking, 22.5 minutes were spent walking with split belts and 7.5 minutes were spent walking with tied-belts. Participants received the same sequence of belt speed perturbations. To confirm

the perception of these belt changes, participants completed a short survey about belt speeds and belt speed changes after the PET imaging was completed.

Figure 6.1A: Example of Step to Step Symmetry in a healthy older adult.

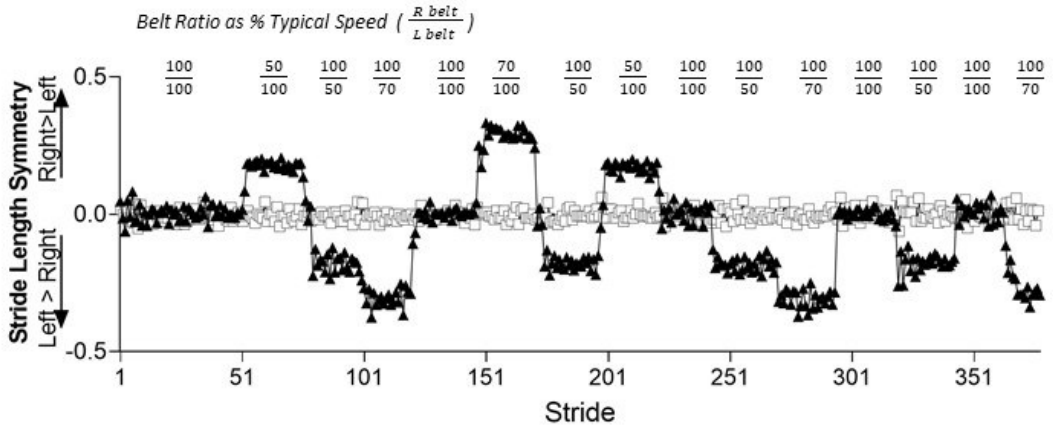


Figure 6.1B: Example of Step to Step Symmetry in an adult with Parkinson's disease.

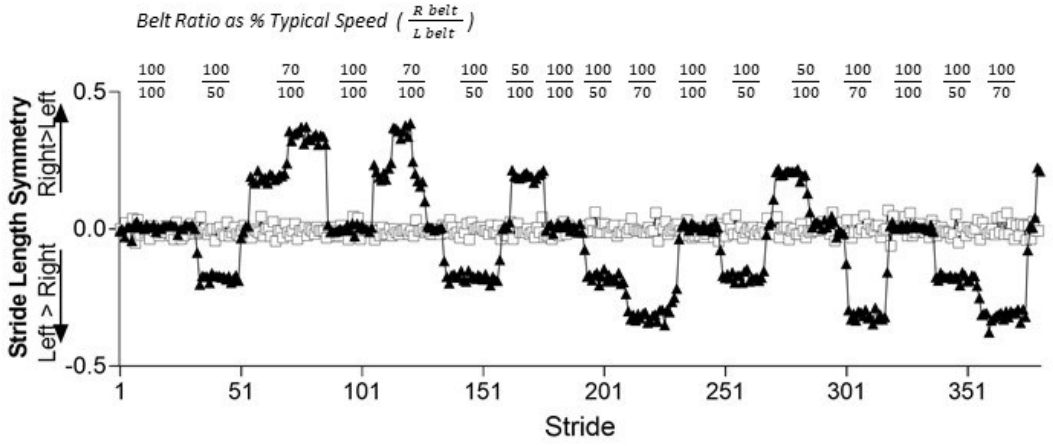


Figure 6.1: Example of Step-to-Step Symmetry in A) Healthy Older Adult and B) Adult with Parkinson's disease. *While both belts remained at the participant's typical walking speed during tied-belt (gray squares), the belt speed ratio was changed every 30 seconds during the continuous adjustment condition (black triangles). The right and left belt speeds during the continuous adjustment condition are displayed as a ratio of typical speed, where 100 is equal to typical walking speed. Belt speeds were set at 50%, 70% or 100% of typical walking speed during the continuous adjustment condition. Stride length symmetry is displayed as a ratio between legs where 0 represents completely symmetric walking.*

PET and Magnetic Resonance Image (MRI) Acquisition

PET image acquisition began within 50 minutes of injection (PD: 49±2 minutes; Control: 49±2 minutes). This delay included the completion of the treadmill walking session (30 minutes), and a transition period for the participants to walk to the Positron Emission Tomography (PET) Imaging Centre at the Montreal Neurological Institute (MNI) (PD: 5±2 minutes, Control: 6±3 minutes). Actual PET scan acquisition time was 40 minutes in duration followed by an additional 10 minutes of transmission time for attenuation correction. The combined walking time, transition and imaging time was within the 110-minute half-life of ^{18}F-FDG tracer (PD: 99± 2 minutes, Control 99± 2 minutes).

Images were obtained with a High-Resolution Research Tomograph (HRRT) PET scanner (CTI/Siemens, Knoxville, Tennessee) with a spatial resolution of 2.3-3.4 mm at full width half maximum (Funck, Paquette et al. 2014). 3D sinograms were produced from the list-mode data acquired over 40 minutes and reformatted in a series of 8 successive 3D images summed over 5 minutes each. The use of 8 consecutive static images allowed for motion artefact correction. The 8 frames were then summed into a single 40-minute long frame.

T1-weighted anatomical images of the brain were acquired for co-registration with PET images on a Siemens Time Trio 3 Tesla Scanner (Siemens, Knoxville, TN). A 3D magnetization rapid gradient echo was used (echo time: 2.98 ms; repetition time: 23 ms, flip angle = 9°) resulting in a voxel size of 1 X 1 X 1 mm obtained across the entire brain using an echoplanar imaging sequence (field of view = 240 x 256 mm^2).

PET Image Analysis: Preprocessing

All PET images were processed and compared using Statistical Parametric Mapping 12 (SPM12, Welcome Trust Centre for Neuroimaging, Institute of neurology, University College London, London, UK) running within MATLAB 2014b (MathWorks, Natick, Massachusetts, USA). Each condition's image was then linearly co-registered to the participant's native T1-weighted MR anatomical image. That MR study was co-registered and spatially normalized to the Montreal Neurological Institute template ICBM 152 6th generation linear brain atlas (Mazziotta, Toga et al. 2001). The affine transformation (12 parameter for rigid transformations (Friston, Ashburner et al. 1995), allowing for co-registration of the subject's MR study to the template, was then applied to the PET images already co-registered to the subject's MR in native space. Both PET images were then transformed into the MNI template space in a spatially normalized format. Using a Gaussian filter (Full width half Maximum = 8mm), normalized PET images were blurred to increase signal-to-noise ratio. Radioactivity levels were then normalized to the radioactivity detected in the white matter using a mask of the centrum semiovale in MNI space, generating white matter-normalized Standardized Uptake Value Ratios (SUVRs). This step was used to remove the effects of inter-subject, non-test condition linked differences in FDG counts prior to voxel based statistics (la Fougere, Zwergal et al. 2010).

PET Image Statistical Analysis

Whole Brain: The main outcome measures to assess changes in brain activity during continuous walking adjustment as compared to the tied-belt condition were regional SUVRs. To determine which brain regions are involved in the continuous alteration of the gait pattern, a flexible factorial design in SPM12 was used with treadmill condition (tied-belt, continuous adjustment) and group (healthy older adults, adults with PD) as the dependent variables with

treadmill being a repeated condition. Whole-brain group contrasts indicating clusters of voxels of significant increase or decrease in glucose metabolism were identified ($p<0.005$, minimum 30 contiguous voxels, uncorrected; Tard, Delval et al. 2015). Activity was normalized to a global mean value of 50. All stereotactic coordinates refer to the MNI coordinate system.

Gait Analysis

The spatiotemporal gait outcomes analyzed were obtained directly from the Mobility Lab™ algorithms of the iWalk plugin for each gait cycle. To assess control of the foot throughout the gait cycle, foot strike angle (degrees between the ground and the toes at initial heel contact); and toe off angle (degrees between the ground and the heel at toe off) were assessed across the entire 30-minute trial. Stride length (meters from heel contact to heel contact of the same leg) and the proportion of the gait cycle spent in dual support provided a more global measure of each gait cycle's spatial and temporal aspects. A relative measure of dual support was calculated based on which leg was approaching terminal stance: for instance left leg dual support occurred from right-foot heel contact to left-foot toe-off (Reisman, Block et al. 2005). Dual support for each leg was then expressed as a proportion of the gait cycle (% GCT).

Gait symmetry was assessed as the difference in performance in terms of stride length and dual support between each leg, presented as a ratio of the combined performance of both legs for that gait cycle (Equation 1).

Equation 1:

$$Symmetry = \frac{Right\ Leg - Left\ Leg}{Right\ Leg + Left\ Leg}$$

Symmetry values ranged from -1 to 1 where a value of 0 indicates both legs performed at exactly the same level. A positive symmetry value indicates the right leg showed a longer stride

length or larger proportion of dual support and a negative symmetry value indicates the left leg showed a longer stride length or larger proportion of dual support (Malone and Bastian 2010).

Each participant's global mean and standard deviation of stride length symmetry and dual support symmetry were calculated across the entire 30-minute trial to compare treadmill conditions and between groups. To further describe global stride-to-stride variability of symmetry measures, the proportion of steps (%total) each participant took beyond 2 standard deviations of the tied-belt mean was calculated for both the tied-belt walking and continuous adjustment trial. To describe motor control of the foot, each participant's global mean of foot strike angle and toe off angle of each foot were calculated across the entire 30-minute trial to compare treadmill conditions and between groups.

Gait Outcomes Statistical Analysis

To determine overall differences in gait symmetry between treadmill conditions, six one-way mixed measures ANOVA's were used to detect an effect of group (healthy older adults, PD) and treadmill trial type (tied-belt, continuous adjustment; repeated measure) for overall mean, standard deviation and number of steps outside 2 standard deviations threshold for dual support and stride length symmetry. To determine differences in mean of foot strike angle and toe off angle for each foot, two three way ANOVA's were used to detect an effect of group (healthy older adults, PD), treadmill trial type (tied-belt, continuous adjustment; repeated measure) and foot (dominant vs non-dominant for healthy older adults, affected vs non affected in participants with PD). Statistical tests were completed in GraphPad Prism (Version 8.2) and deemed significant at $p<0.05$.

6.4 Results

Participant groups were matched in age (PD: 65±5 years, Control: 66±4 years), treadmill walking speed (PD: 0.9±0.2 m/s, Control: 0.9±0.1 m/s) and MOCA score (PD: 26±2, Controls: 27±2 all n.s., see Table 6.1). Participants with PD reported being able to function in their daily activities independently. They performed similarly on the UPDRS clinical assessment in both ON and OFF medication states (ON: 35±9; OFF: 32±5, $p>0.05$) and were deemed a Hoehn & Yahr rating of 2 to 3. All participants were right hand and right foot dominant. Participants with PD reported their most affected side as their right side most often (n=9 right side most affected, n=1 left side most affected).

Gait Symmetry

Overall gait symmetry was centred around 0 for both tied-belt and continuous adjustment protocols, a level of symmetry typically associated with straight, symmetrical walking (Figure 6.2A, 2B). The continuous adjustment trial was balanced so that changes to right and left belts were equal. There were no significant differences in overall mean dual support symmetry between healthy older adults and adults with PD, or between the tied-belt and continuous adjustment protocols ($p>0.05$, Figure 6.2A). While there was a statistically significant difference between treadmill conditions for stride length symmetry (main effect of treadmill ($F(1,15)=6.652$, $p=0.0209$), the mean of both conditions was less than 0.01. Finally, while there was a statistically significant difference between groups for stride length symmetry (main of group ($F(1,18)=7.735$, $p=0.0143$), again the mean of both groups was small, less than 0.01. The fact that the overall means were so low indicates a lack of functional difference in gait symmetry either between treadmill protocols or groups that may be expected over 30 minutes of walking.

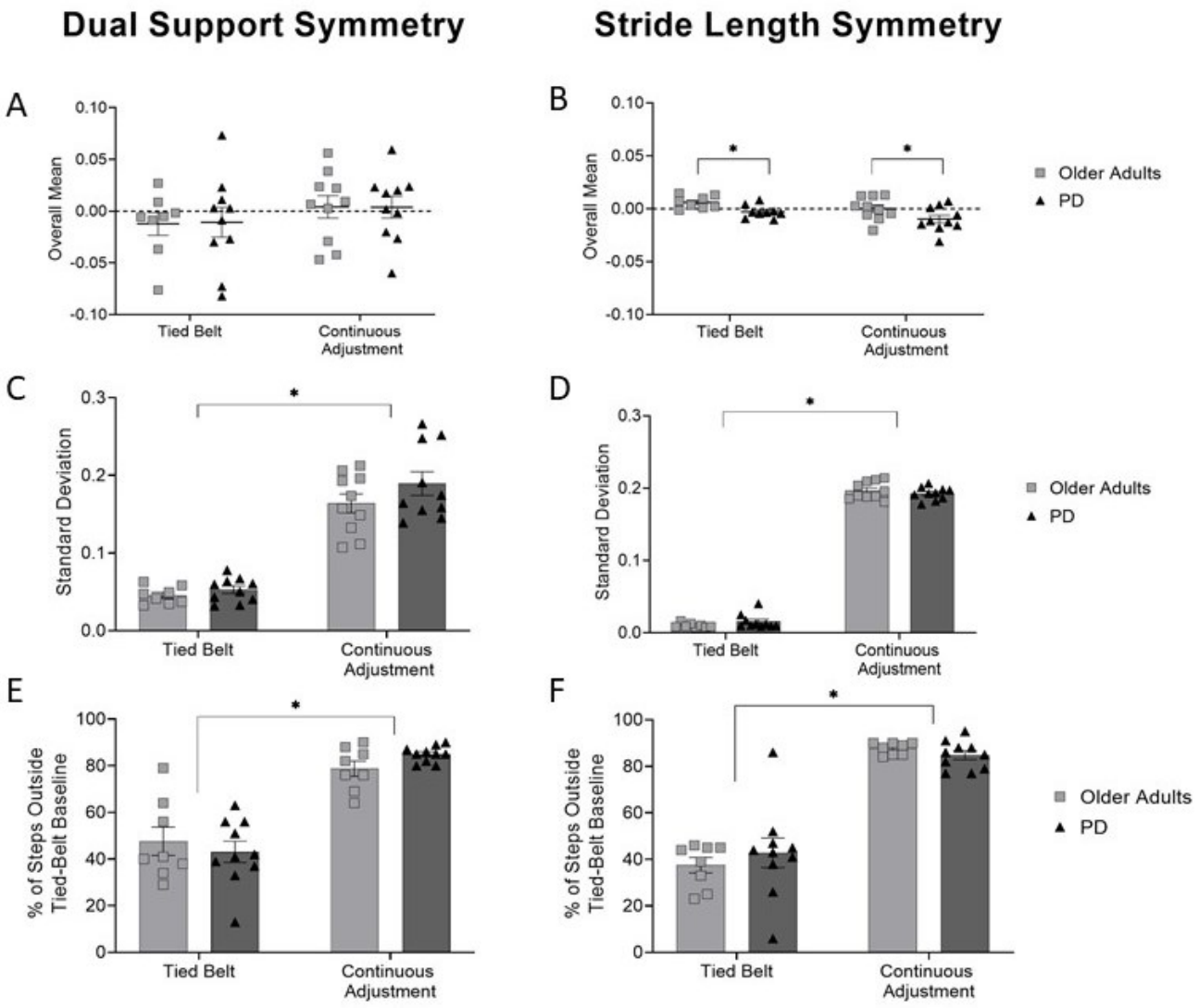


Figure 6.2: Gait Symmetry. *Individual data points represent each participant. The group mean ± 1SE is represented with a solid line. Gait symmetry was measured using a temporal outcome (time spent in dual support (A, C, E) and spatial outcome (stride length (B, D, F) where a value of 0 is completely symmetric walking. An overall mean for each measure across the entire 30 minutes trial is displayed in panels A and B. The overall variability (as a standard deviation) is presented in panels C and D. Finally, a measure of each participant's relative variability is displayed in panels E and F as the percentage of steps outside of their baseline (mean ±SD) during the tied-belt trial.*

Gait Variability

While overall mean performance of dual support symmetry and stride length symmetry were similar across both trials, variability significantly differed between trial types but not groups (Figure 6.2C-F). Overall variability (standard deviation of gait symmetry measures) was greater during the continuous adjustment trial than the tied belt trial (Figure 6.2C: main effect of treadmill $F(1,16)=171.2$, $p<0.0001$; Figure 6.2D: main effect of treadmill $F(1,16)=4581$, $p<0.0001$). In further support of this finding, both groups spent a greater percentage of steps outside their tied-belt baseline (mean of tied belt±2SD) during the continuous adjustment trial (Figure 6.2E: main effect of treadmill $F(1,15)=120.7$, $p<0.0001$; Figure 6.2F: main effect of treadmill $F(1,15) = 415.4$, $p<0.0001$).

Control of Heel Contact and Toe Off

Both participant group and treadmill trial protocol affected the control of heel contact. Participants in both groups decreased foot strike angle at heel contact (i.e. reduced dorsiflexion) of both feet during the continuous adjustment trial (Figure 6.3A: main effect of treadmill $F(1,32) = 11.89$, $p = 0.0016$). Older adults had a larger foot strike angle at heel contact (i.e. greater dorsiflexion) of both feet than adults with Parkinson's disease (Figure 6.3A, main effect of group $F(1,36) = 9.577$, $p=0.0038$). The treadmill trial protocol affected the control of toe off as all participants decreased heel pickup during the continuous adjustment trial compared to the tied-belt trial (Figure 6.3B, main effect of treadmill $F(1,32) = 58.20$, $p<0.0001$). There was no significant difference between participant groups for toe off angle for either foot ($p>0.05$).

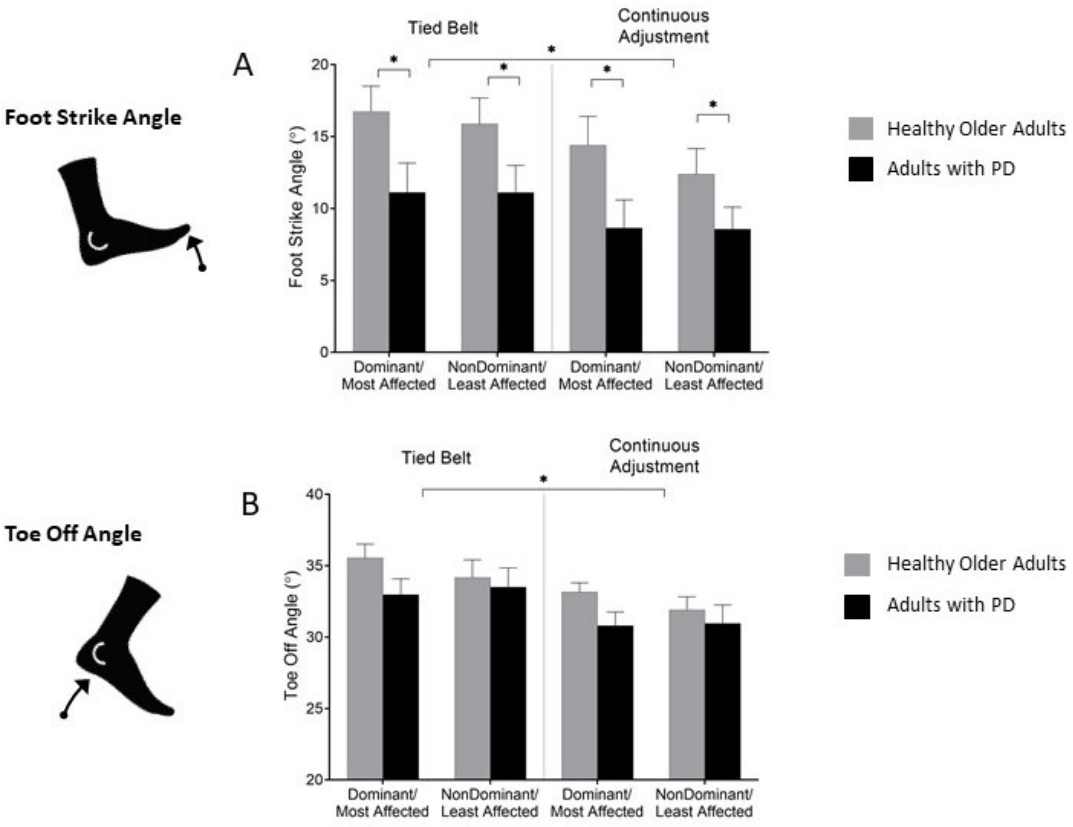


Figure 6.3: Foot Strike and Toe off Angle. *The group mean ± 1SE is represented with a solid line.* ***A)*** *Foot strike angle (i.e. the amount of dorsiflexion at heel contact) of each foot (Dominant/Nondominant for healthy older adults; Most affected/Least affected in adults with PD).* ***B)*** *Toe-off angle (i.e. the amount of heel pickup at toe off) of each foot (Dominant/Nondominant for healthy older adults; Most affected/Least affected in adults with PD).*

Brain Activation in Older Adults: continuous adjustment vs tied-belt

Increased peak activation during continuous adjustments to the gait pattern (in comparison to tied-belt treadmill walking) were found within visual and auditory cortices, frontal medial cortex and the temporal fusiform cortex in healthy older adults. ($p<0.005$, uncorrected, Figure 6.4, Table 6.2).

Decreased activation during continuous adjustments to the gait pattern (compared to tied-belt treadmill walking) was found within a cluster in the superior parietal lobule (BA 7; $p<0.05$ FWE corrected) and significantly decreased peak activation in the primary and secondary somatosensory (BA 1,2,3) and primary motor areas (BA 4), Broca's area, cingulate gyrus, left pallidum, inferior temporal gyrus and frontal pole. In addition, a significant decrease in peak activation were found in the brain stem, cerebellum (Right Lobule V), corticospinal tract, fornix and callosal body ($p<0.005$, uncorrected; Figure 6.5, Table 6.3).

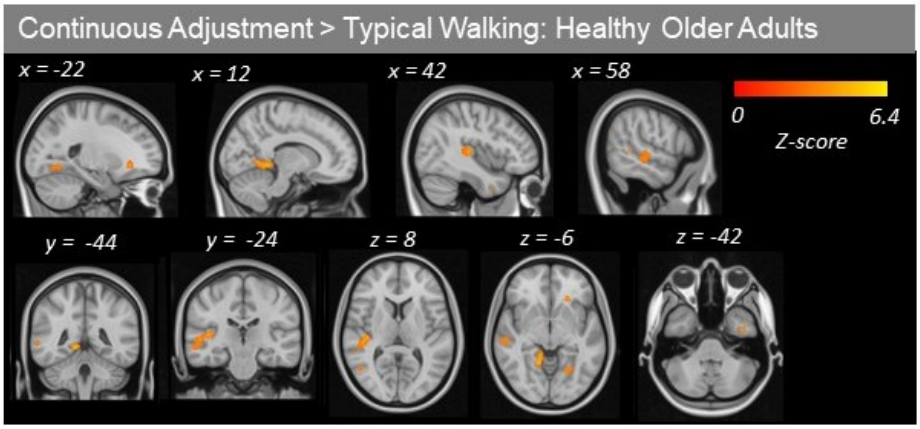


Figure 6.4: Activation maps for increased [^{18}F]-FDG uptake during continuous adjustments (vs tied belt) in healthy older adults. *Compared to tied-belt walking, continuous adjustments to the gait pattern significantly increased peak glucose uptake within visual and auditory cortices, frontal medial cortex and the temporal fusiform cortex in healthy older adults (whole brain, $p<0.005$, uncorrected, cluster minimum 30 voxels).*

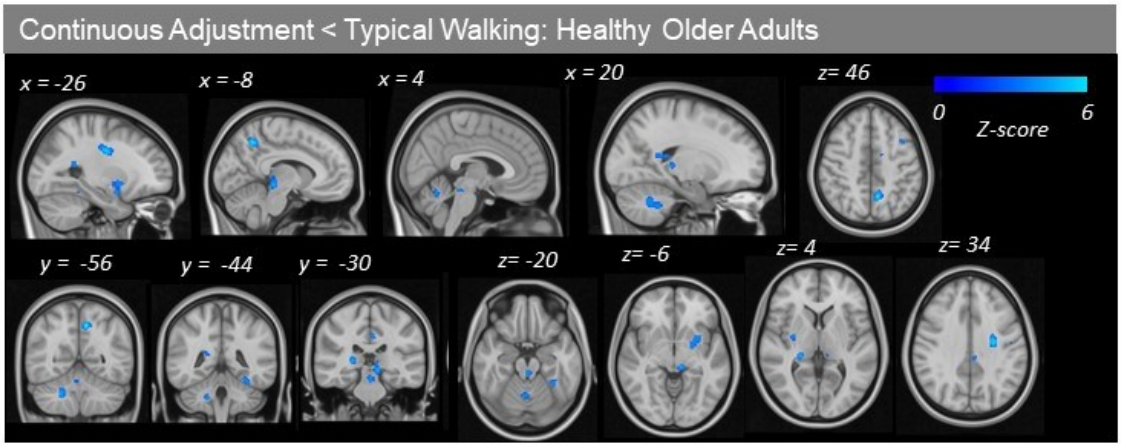


Figure 6.5: De-activation maps for decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied belt) in healthy older adults. *Compared to tied-belt, continuous adjustments to the gait pattern significantly decreased glucose uptake within a cluster in the superior parietal lobule (BA 7) and significantly decreased peak glucose in the primary and secondary somatosensory (BA 1,2,3) and primary motor areas (BA 4) and cerebellum (Right Lobule V) (whole brain, p<0.005, uncorrected, cluster minimum 30 voxels).*

Brain Activation in Adults with PD: continuous adjustment vs tied-belt

Increased peak activation during continuous adjustments to the gait pattern (in comparison to tied-belt treadmill walking) were found within medial and inferior frontal gyri, supplementary and primary motor area, posterior parietal cortex, posterior cingulate and right and left cerebellum (Lobule I-IV; p<0.005, uncorrected, Figure 6.5, Table 6.4). In addition, a significant increase in peak activation occurred in the corticospinal tract and fornix (p<0.005, uncorrected, Figure 6.6, Table 6.4).

Decreased peak activation during continuous adjustments to the gait pattern (in comparison to the tied-belt treadmill waking) were found within the primary auditory and primary and secondary visual cortices, the inferior parietal cortex, the inferior temporal gyrus, and the insular cortex (p<0.005, uncorrected, Figure 6.7, Table 6.5). In addition, a significant peak decrease in

activation was found in the optic radiation and left thalamus ($p<0.005$, uncorrected). Finally, a significant peak decrease in activation was found in the left cerebellum (Lobule VI).

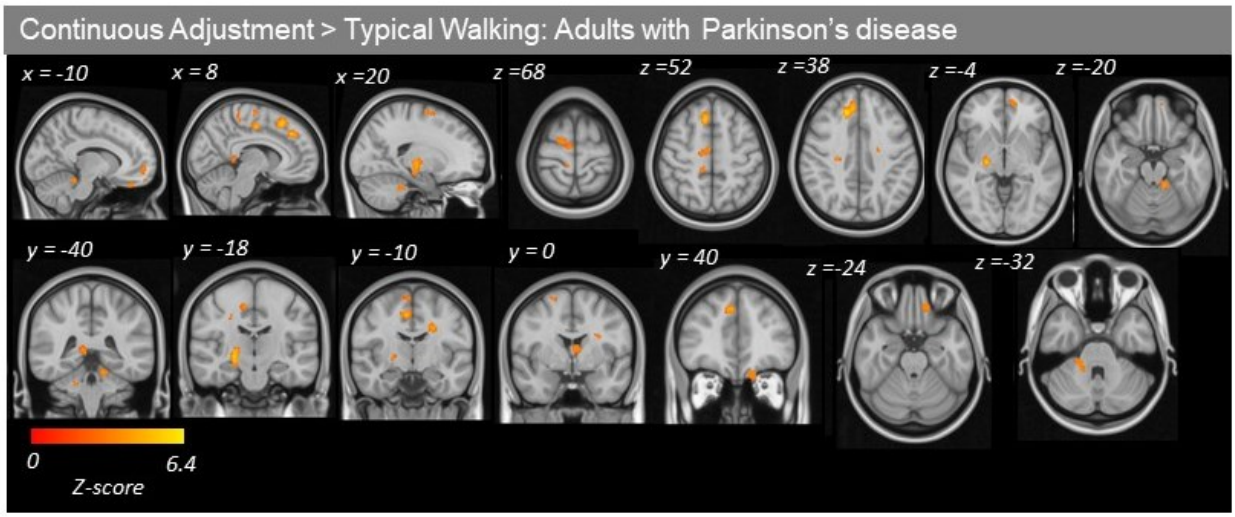


Figure 6.6: Activation maps for increased [^{18}F]-FDG uptake during continuous adjustments (vs tied belt) in adults with Parkinson's disease. *Compared to tied-belt, continuous adjustments to the gait pattern significantly increased peak glucose uptake supplementary and primary motor area, posterior parietal cortex, posterior cingulate and right and left cerebellum (Lobule I-IV; whole brain, $p<0.005$, uncorrected, cluster minimum 30 voxels)*

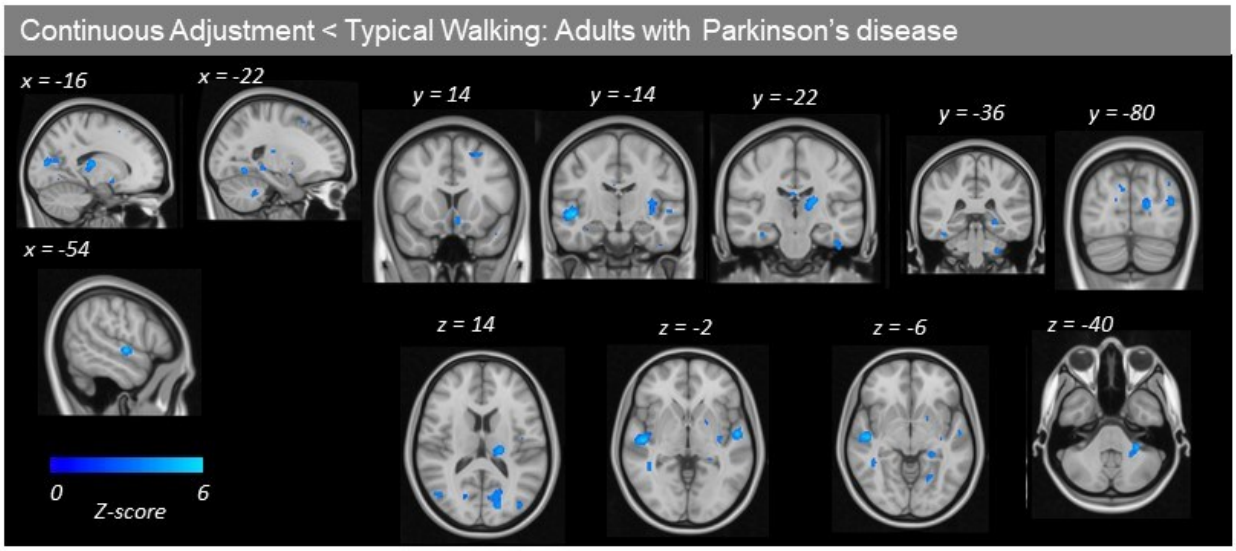


Figure 6.7: De-activation maps for decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied belt) in adults with Parkinson's disease. *Compared to tied-belt, continuous adjustments*

to the gait pattern significantly decreased peak glucose uptake within the primary auditory and primary and secondary visual cortices, the inferior parietal cortex, the inferior temporal gyrus, and the insular cortex and in the left cerebellum (Lobule VI, p<0.005, uncorrected, cluster minimum 30 voxels).

Brain activation during Continuous Adjustments: PD>Older Adult

Increase activation during continuous adjustments to the gait pattern for adults with Parkinson's disease (compared to healthy older adults) was found in a cluster within the premotor, supplementary and primary motor areas ($p<0.001$ FWE corrected, Table 6.6, Figure 6.8). In addition, a significant increase in peak activation within the posterior parietal cortex, Broca's area, inferior parietal lobule, and primary somatosensory areas and left cerebellum (Lobule VIIIb; $p<0.005$ uncorrected).

Brain activation during Continuous Adjustment: Older Adult>PD

Decreased peak activation during continuous adjustments to the gait pattern for adults with Parkinson's disease (compared to healthy older adults) were found in the anterior intraparietal sulcus, secondary visual cortices and the optic radiation ($p<0.005$, uncorrected; Figure 6.9, Table 6.7).

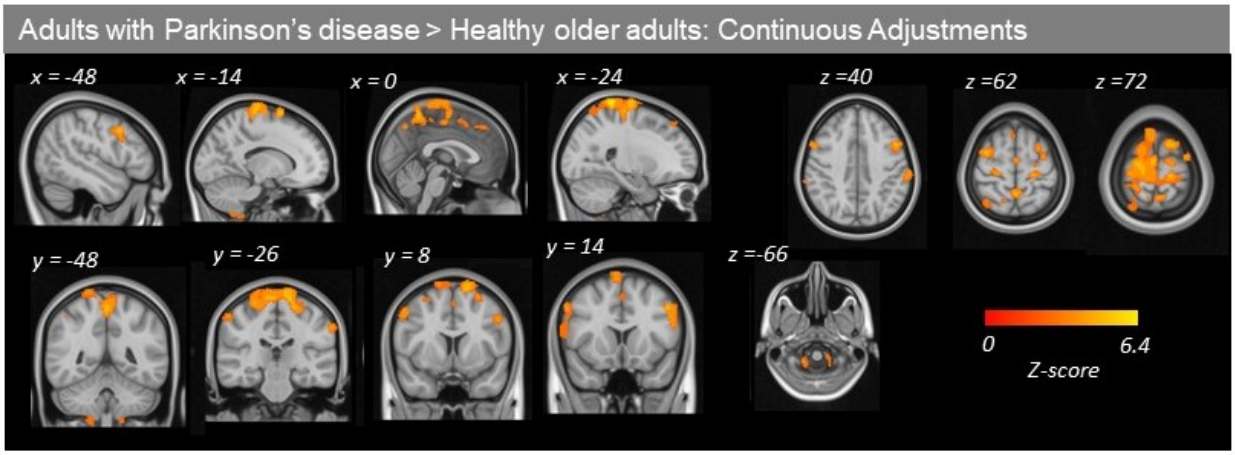


Figure 6.8: Activation maps for increased [^{18}F]-FDG uptake in adults with Parkinson's disease during continuous adjustments of the gait pattern. *Compared to healthy older adults, continuous adjustments to the gait pattern for adults with Parkinson's disease significantly increased glucose uptake within a cluster in the premotor, supplementary and primary motor areas (p<0.001 FWE corrected). In addition, a significant increase in peak glucose uptake occurred within the posterior parietal cortex, inferior parietal lobule, and primary somatosensory areas and left cerebellum (Lobule VIIIb; p<0.005, uncorrected, cluster minimum 30 voxels).*

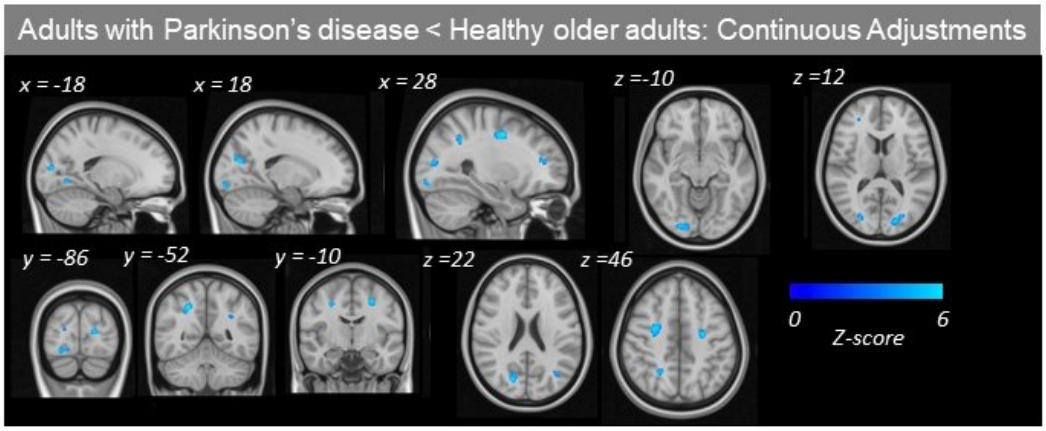


Figure 6.9: De-activation maps for decreased [^{18}F]-FDG uptake in adults with Parkinson's disease during continuous adjustments of the gait pattern. *Compared to healthy older adults, continuous adjustments to the gait pattern for adults with Parkinson's disease have significantly decreased peak activation in the anterior intraparietal sulcus, secondary visual cortices and the optic radiation (p<0.005, uncorrected, cluster minimum 30 voxels).*

Table 6.2: Increased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking) in healthy older adults. Whole Brain, voxel p<0.005 (uncorrected), cluster minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Right Lingual Gyrus – Visual Cortex		0.968	0.092	227	5.59	4.71	0.072	0	16	-52	-4
					4.55	4.02	0.631	0	12	-44	-4
Right Temporal Gyrus – Primary Auditory	41, 42	0.741	0.036	373	4.65	4.09	0.543	0	50	-28	4
					3.94	3.57	0.981	0	42	-24	8
					3.59	3.29	1	0	58	-26	-6
Left Frontal medial cortex		1	0.444	45	3.76	3.43	0.997	0	-8	52	-14
Left Temporal Fusiform Cortex,		1	0.538	30	3.74	3.42	0.998	0	-36	-6	-42
Right Lateral occipital cortex – visual cortex V5	19	1	0.35	66	3.74	3.41	0.998	0	48	-62	10
					3.35	3.1	1	0.001	48	-70	14
Left Lingual gyrus – visual cortex V3, V4	19	1	0.319	75	3.56	3.27	1	0.001	-22	-62	-6
					3.25	3.02	1	0.001	-22	-70	-10
White Matter											
		1	0.455	43	4.13	3.71	0.926	0	-22	28	-6

Table 6.3: Decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking) in healthy older adults. Whole Brain, p<0.005, minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Left Superior parietal lobule	7	1	0.217	116	6.06	5	0.022	0	-8	-56	46
Left Primary somatosensory Primary motor	3,4	1	0.418	50	4.09	3.68	0.942	0	-50	-10	30
Left Middle frontal gyrus		1	0.455	43	4.01	3.62	0.967	0	-38	10	50
Broca's area					2.87	2.7	1	0.003	-42	14	38
Left Cingulate gyrus		1	0.51	34	3.8	3.46	0.995	0	-2	-32	38
Left pallidum		0.988	0.117	193	3.8	3.46	0.995	0	-22	-2	-4
					3.63	3.33	1	0	-30	8	-6
Left Inferior Temporal Gyrus					3.53	3.25	1	0.001	-26	4	-16
		1	0.496	36	3.79	3.46	0.996	0	-50	-18	-34
Right Secondary somatosensory		1	0.433	47	3.75	3.42	0.998	0	32	-6	8
Left Temporal Fusiform Cortex		1	0.391	56	3.37	3.12	1	0.001	-32	-44	-20
Left Frontal Pole		1	0.472	40	3.17	2.95	1	0.002	-22	58	10
Subcortical Structures											
Left Brain Stem		0.997	0.157	155	4.2	3.76	0.893	0	-8	-30	-6
					3.8	3.46	0.996	0	0	-30	-18
White Matter											
Corticospinal Tract		0.999	0.191	131	5.39	4.58	0.119	0	-26	-10	34
Fornix		1	0.215	117	4.41	3.92	0.748	0	24	-32	4
					3.38	3.13	1	0.001	20	-46	16
		1	0.202	124	4.28	3.82	0.844	0	22	-56	-36
					3.54	3.26	1	0.001	20	-46	-40
Callosal Body		1	0.354	65	3.58	3.29	1	0.001	-30	-48	16
		1	0.478	39	3.23	3	1	0.001	-16	0	40
Cerebellum											
Cerebellum – Right V		1	0.386	57	3.38	3.13	1	0.001	4	-58	-20

Table 6.4: Increased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking) in adults with Parkinson's disease. Whole Brain, voxel p<0.005 (uncorrected), cluster minimum 30 voxels.

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Right Medial Frontal Gyrus (Supplementary Motor Area)	6	0.64	0.027	421	5.78	4.83	0.046	0	16	32	38
	6				5.12	4.41	0.219	0	8	24	52
					4.67	4.1	0.523	0	8	38	38
Left Medial Frontal Gyrus (Frontal Pole)		0.938	0.265	94	3.61	3.31	1	0	-10	56	-4
					2.98	2.8	1	0.003	-8	56	-18
Left Inferior Frontal Gyrus (Frontal Pole)		0.938	0.329	72	3.53	3.25	1	0.001	-12	40	-24
Right Superior/Medial Frontal Gyrus (Supplementary Motor Area)	6	0.999	0.183	136	4.58	4.04	0.604	0	8	-10	48
					3.88	3.52	0.989	0	14	-16	50
Superior Frontal Gyrus (Supplementary Motor Area)	6	1	0.211	119	3.5	3.23	1	0.001	16	-6	68
	6				3.15	2.94	1	0.002	20	2	64
	6				3.09	2.89	1	0.002	6	-12	66
Left Posterior Parietal	7	1	0.413	51	4.15	3.73	0.919	0	-24	-70	44
Right Post Central Gyrus (Primary Motor Area)	4a		0.386	57	3.5	3.23	1	0.001	10	-32	54
	4a				3.1	2.9	1	0.002	10	-34	68
Right Posterior Cingulate			0.938	54	3.32	3.08	1	0.001	10	-40	4
White Matter											
Corticospinal Tract		0.993	0.13	179	5.23	4.48	0.173	0	22	-18	-6
Corticospinal Tract		1	0.213	118	4.01	3.62	0.966	0	-22	-10	32
					3.62	3.32	1	0	-26	-4	26
Corticospinal Tract		1	0.51	34	3.8	3.46	0.995	0	26	-20	38
Fornix		1	0.362	63	3.62	3.32	1	0	-2	0	10
Cerebellum											
L Cerebellum Lobule I- IV		1	0.404	53	3.72	3.4	0.998	0	-12	-40	-20
R Cerebellum Lobule I-IV			0.358	64	3.51	3.23	1	0.001	20	-36	-32

Table 6.5: Decreased [^{18}F]-FDG uptake during continuous adjustments (vs tied-belt walking) in adults with Parkinson's disease. Whole Brain, p<0.005, minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Left Temporal Occipital Fusiform		0.992	0.128	181	5.69	4.78	0.056	0	-34	-54	-14
Right Primary Auditory		0.982	0.106	206	5.61	4.73	0.069	0	50	-14	-4
Left Primary Auditory		1	0.273	91	4.76	4.16	0.451	0	-54	-10	0
Left Inferior Temporal Gyrus		1	0.316	76	4.18	3.75	0.901	0	-44	-20	-32
Left Lingual Gyrus – Visual Cortex		1	0.374	60	4.02	3.63	0.964	0	-20	-60	-8
Left Sub Callosal Cortex		1	0.391	56	3.86	3.51	0.991	0	-4	12	-10
Left Inferior Parietal – Lateral Occipital Cortex		1	0.391	56	3.77	3.44	0.997	0	-40	-80	16
Left Visual Cortex	17	0.99	0.123	186	3.75	3.42	0.997	0	-16	-80	14
	17				3.35	3.1	1	0.001	-14	-68	16
Right Hippocampus cornu ammonis, dentate gyrus, temporal fusiform cortex		1	0.292	84	3.74	3.42	0.998	0	34	-18	-20
					3.7	3.38	0.999	0	36	-30	-22
					3.17	2.96	1	0.002	42	-38	-20
Right Inferior Parietal – Lateral Occipital Cortex		1	0.46	42	3.61	3.31	1	0	48	-70	14
Left Inferior Temporal Gyrus		1	0.516	33	3.57	3.28	1	0.001	-50	-50	-18
Left Temporal Pole		1	0.484	38	3.55	3.26	1	0.001	-46	8	-18
Right Callosal body – cingulate gyrus		1	0.37	61	3.46	3.19	1	0.001	8	-8	28
					3.1	2.9	1	0.002	4	-20	22
Left Hippocampus		1	0.503	35	3.45	3.18	1	0.001	-22	-36	-6
Left Inferior Parietal – Lateral Occipital Cortex		1	0.484	38	3.37	3.12	1	0.001	-38	-76	32
Right Secondary Visual Cortex	18	1	0.516	33	3.33	3.09	1	0.001	10	-84	30
Left Insular cortex		1	0.275	90	3.29	3.05	1	0.001	-34	-14	-2
					3.26	3.03	1	0.001	-34	-14	8
					2.87	2.71	1	0.003	-40	-10	12
Left Frontal orbital cortex		1	0.496	36	3.22	3	1	0.001	-18	4	-12
					2.86	2.7	1	0.003	-18	4	-2
Left Middle frontal gyrus – premotor area	6	1	0.53	31	3.17	2.96	1	0.002	-26	14	54
Subcortical Structures											
Left Thalamus		0.987	0.116	194	4.22	3.78	0.884	0	-18	-22	14
					4.16	3.74	0.911	0	-14	-26	6

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
White Matter											
Optic radiation		1	0.478	39	3.45	3.18	1	0.001	44	-44	-4
Optic radiation		1	0.466	41	3.28	3.04	1	0.001	20	-72	16
					2.82	2.66	1	0.004	16	-82	20
Cerebellum											
Cerebellum – Left VI		1	0.273	91	4.57	4.03	0.608	0	-28	-40	-40

Table 6.6: Increased [^{18}F]-FDG uptake during continuous adjustments in adults with Parkinson's disease (vs. healthy older adults). Whole Brain, voxel p<0.005 (uncorrected), cluster minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Right Precentral gyrus	4	0	0	4852	6.42	5.21	0.009	0	24	-40	80
Left Premotor, supplementary motor, primary motor area	6				6.18	5.07	0.016	0	4	-12	80
					5.7	4.78	0.055	0	12	-20	76
Left Broca's area	44	0.868	0.054	307	4.85	4.23	0.381	0	-48	12	40
					4.07	3.67	0.95	0	-52	14	28
					3.6	3.31	1	0	-54	12	20
Right Precentral gyrus, posterior parietal	4, 5,	0.492	0.018	495	4.67	4.1	0.523	0	0	-48	62
	7				3.31	3.07	1	0.001	4	-30	56
Right Middle frontal gyrus		0.978	0.101	213	4.38	3.89	0.774	0	36	2	62
Right Premotor cortex, Broca's area	6	0.682	0.03	401	4.35	3.87	0.796	0	54	10	44
	44,45				3.56	3.27	1	0.001	60	18	20
					3.51	3.24	1	0.001	58	26	24
Left Inferior parietal lobule		0.982	0.107	205	3.82	3.48	0.994	0	-64	-26	40
Right Inferior Temporal Gyrus		1	0.358	64	3.66	3.35	0.999	0	48	-14	-42
Right Post central gyrus, inferior parietal lobule, supramarginal gyrus		0.931	0.071	264	3.52	3.24	1	0.001	60	-22	52
					3.09	2.89	1	0.002	56	-34	52
					2.86	2.7	1	0.003	68	-34	40
Right Posterior parietal	7	1	0.496	36	3.4	3.14	1	0.001	2	-68	48
Left Primary somatosensory	1	1	0.319	75	3.34	3.1	1	0.001	-58	-14	48
**		1	0.211	119	3.31	3.07	1	0.001	20	-52	-66
Right Frontal Pole		1	0.466	41	3.28	3.05	1	0.001	48	56	6
Midline Superior Frontal Gyrus		1	0.49	37	3.25	3.02	1	0.001	0	40	46
					2.8	2.65	1	0.004	2	28	48
Midline Supplementary Motor	6	1	0.433	47	3.11	2.91	1	0.002	0	6	54
	6				3.03	2.84	1	0.002	0	14	50
Right Premotor	6	1	0.53	31	3.1	2.9	1	0.002	24	40	52
Cerebellum											
Cerebellum left VIIIb		1	0.251	100	3.24	3.01	1	0.001	-16	-56	-62
					2.97	2.79	1	0.003	-14	-44	-64

Table 6.7: Increased [^{18}F]-FDG uptake during continuous adjustments in healthy older adults (vs. adults with Parkinson's disease). Whole Brain, voxel p<0.005 (uncorrected), cluster minimum 30 voxels

		Cluster			Peak						
Brain Region	BA	Q FWE Corr	P uncorr	Cluster size	t	Z	Q FWE-corr	P uncorr	X	Y	Z
Grey Matter											
Right Anterior intraparietal sulcus		1	0.3	81	4.75	4.16	0.462	0	24	-52	42
Right Premotor/ supplementary motor	6	0.999	0.191	131	4.65	4.09	0.539	0	28	-4	44
Right Visual cortex V2-	18	1	0.292	84	4.15	3.73	0.916	0	18	-74	22
Right Visual Cortex V2	18	1	0.273	91	3.98	3.6	0.973	0	24	-88	-10
Left Premotor/supplementary motor	6	1	0.322	74	3.9	3.54	0.987	0	-24	-10	46
Right Frontal Pole		1	0.472	40	3.78	3.45	0.996	0	30	40	16
Left Visual Cortex V3,V4		1	0.404	53	3.52	3.24	1	0.001	-18	-66	-4
Left Inferior Parietal – Lateral Left Occipital Cortex		1	0.295	83	3.46	3.19	1	0.001	-34	-68	26
					3.11	2.91	1	0.002	-32	-50	30
Right Premotor – Frontal Pole	6	1	0.53	31	3.1	2.9	1	0.002	24	40	52
White Matter											
Optic Radiation		1	0.319	75	3.88	3.53	0.989	0	-18	-86	12
					3.37	3.12	1	0.001	-26	-80	12
Optic Radiation		1	0.472	40	3.34	3.1	1	0.001	26	-80	12

6.5 Discussion:

^{18}F-FDG PET imaging during split belt treadmill walking adults with PD off dopamine medication increased use of motor planning areas during continuous gait adjustments beyond recruitment levels seen in older adults. While we determined that all participants were able to rapidly adjust their gait pattern to the belt speed changes, participants with PD had reduced dorsiflexion at heel contact and reduced heel pickup at toe off, indicating a more flat-footed approach during the continuous adjustment protocol than healthy older adults. We propose that an over excitation of the inhibitory tone of the basal ganglia on the cortex due to Parkinson's disease leads to cortical compensation to accommodate the complex walking task and an increase in the requirements for sensory feedback to inform the ongoing locomotor plan (Figure 6.10).

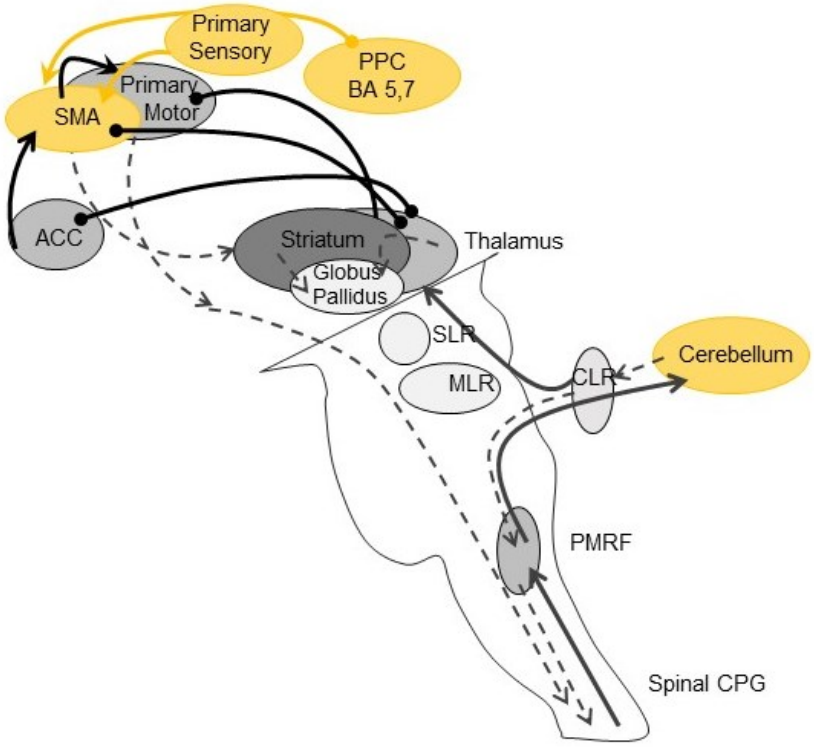


Figure 6.10: The effects of Parkinson's disease on the "fine-tuning" network of locomotion. (Adapted from Hinton, Thiel et al. 2019 and la Fougere, Zwergal et al. 2010.

Parkinson's disease causes a reduced output from the basal ganglia, disrupting the network of cortical areas involved in walking. During step-to-step gait pattern changes, Parkinson's disease increased activity (yellow) of cortical regions compared to typical walking (grey). This model elaborates on the "fine tuning network" proposed

by Hinton et al (2019) and the "executive" and "planning" networks of locomotion proposed by la Fougere et al. (2010). SLR: subthalamic locomotor region; MLR: mesencephalic locomotor region; CLR: cerebellar locomotor region; PMRF: pontine and medullary reticular formations; CPG: Central Pattern Generator.

PD altered foot mechanics but not gait symmetry during complex walking

Overall gait variability indicated the continuous adjustment trial created a highly variable environment where all participants were unable to maintain control of gait symmetry as during tied-belt treadmill walking. It is not surprising that participants with PD were able to adjust their gait cycle in a similar manner to healthy older adults (Figure 6.2) as this has been the case across a number of split belt treadmill adaptation protocols (Nanhoe-Mahabier, Snijders et al. 2013, Roemmich, Hack et al. 2014, Roemmich, Nocera et al. 2014, Mohammadi, Bruijn et al. 2015). During overground gait, adults with PD typically walk slower, with shorter strides and more time spent in stance (Morris, Iansek et al. 1994, Bond and Morris 2000). However, on a treadmill, where optic flow is removed, the stance portion of each stride is vital in relaying kinetic and proprioceptive information to the spinal cord and supraspinal feedback integration areas to inform an ongoing motor plan for the locomotion (Hinton, Thiel et al. 2019). In fact, all participants, including those with PD, were able to incorporate enough sensory feedback available to appropriately alter their gait cycle to walk with belts changing speeds and speed ratio between belts on a continuous basis.

While all participants decreased foot strike angle (i.e. reduced dorsiflexion) and toe off angle (i.e. heel pick up) for the continuous adjustment trial, we observed further reductions in foot strike and toe-off angle in participants with PD (Figure 6.3A-B). Foot strike angle during gait is a key indicator of balance control in adults with PD that correlated with more severe clinical scores

of disease related balance impairments (Hasegawa, Shah et al. 2019). We hypothesize a change in foot mechanics to be a compensatory mechanism to reduce attention provided to the fine motor control of the foot. Reduced foot strike angle in adults with PD observed during overground walking was increased with specific instruction to attend to the heel strike portion of the gait cycle (Ginis, Pirani et al. 2017) supporting the hypothesis that it could have been simplified out of the gait pattern during complex walking. A lack of dorsiflexion at heel contact and heel pick up at toe off could indicate a lack of fine movement control, or more likely a compensatory mechanism to overcome the complex task, removing this fine motor control from the overall movement pattern. Overall greater activation of the cortex was observed in adults with PD during the continuous adjustment trial compared to healthy older adults (Figure 6.7), aligning with observations from imagined complex walking which also saw an overall greater activation in adults with PD (Maidan, Rosenberg-Katz et al. 2016). Under the capacity sharing model, if the capacity required for two simultaneous tasks exceeds the overall capacity of attention, performance of one or both tasks will deteriorate (Kahneman 1974, Pashler 1994). As such, it is hypothesized that in order to continue walking with both belts at different speeds, a cortical capacity may have been reached and control of the foot at heel contact was reduced.

A secondary hypothesis related to reduced toe off angle (i.e. reduced heel pickup) is an attempt to reduce time spent in single stance and rush through the swing phase to the next stance and double support phase where the participant is able to gather sensory feedback from the changing belts. Early split belt treadmill work hypothesized a pace making function of the flexor muscles of the leg (e.g. the gastrocnemius, responsible for toe-off) via proprioceptive feedback (Dietz, Zijlstra et al. 1994). Proprioceptive feedback from the gastrocnemius and toe-off phase would then effect tibialis anterior muscle output via spinal circuits, influencing dorsiflexion

required for heel contact to occur (Dietz, Zijlstra et al. 1994). This proprioceptive feedback would be paramount to properly adjusting the next steps to the current belt speed ratio and time spent in stance on each belt would be prioritized over time spent in swing. However, it is hypothesized that a full foot range of motion at heel contact and toe off is advantageous and a potential drawback to reducing foot strike and toe off angle would be a reduction in important tactile and proprioceptive information from the stance. With an increase in disease severity, this could potentially turn into a negative feedback cycle whereby the stance phase no longer has the best sensory feedback, and this lack of feedback signals the foot to continue to move towards a flat-footed, march-like gait cycle and the sensory feedback is further reduced, reducing stride length and continuing a shuffling gait cycle.

Effects of PD on a fine-tuning network for complex walking

PD primarily affects the basal ganglia, where an overexcitation of the basal ganglia's inhibitory tone on cortical motor networks produces jerky movements, tremor, rigidity and inability to produce a smooth walking pattern (Alexander, Crutcher et al. 1990). This becomes even more evident during complex or sequential movements, as was required during the continuous adjustment trial. For instance, during sequential bimanual upper body movements, adults with PD have difficulties in switching between motor tasks and are hypothesized to maintain single tasks within a complex set at discrete motor programs (Benecke, Rothwell et al. 1987). This is further exacerbated with disease progression where freezing of gait, a disease symptom of feeling unable to move despite the participant's initiation to do so, can be observed during complex walking (i.e. turning) or when dual tasking (i.e. walking and walking)(Mitchell, Potvin-Desrochers et al. 2019). Given these disease-related changes to complex movements, we propose a lack of activation from the basal ganglia requires cortical compensations related to sensory feedback in

order for adults with PD to be able to walk on the split belt treadmill during the continuous adjustment trial at the same performance level as healthy older adults (Figure 6.10).

Output from the basal ganglia with PD is altered, however the function of other supraspinal areas involved in locomotion is still intact. Previously, we proposed a fine-tuning network for complex locomotion, with increases in activation in the cerebellum, supplementary motor area, anterior cingulate and posterior parietal cortices compared to typical treadmill walking (Hinton, Thiel et al. 2019). Both the basal ganglia and cerebellum along with lateral premotor areas are activated during learning of a movement (Jueptner, Frith et al. 1997, Jueptner, Stephan et al. 1997) and when motor performance improves (Jueptner, Frith et al. 1997), as in the current task. While basal ganglia activation is related to movement selection from a set of discrete motor programs, the cerebellum utilizes sensory feedback to optimize movement execution (Jueptner and Weiller 1998). Our recent split belt treadmill work in young healthy adults observed activation of lateral cerebellar areas (lobules V, VI) during gait adjustments to treadmill belt speed changes (Hinton, Thiel et al. 2019). The posterior cerebellum, and not the basal ganglia, is more active when movements are performed under sensory guidance only (Jueptner, Jenkins et al. 1996, Jueptner, Ottinger et al. 1997) and is highly reliant on sensory feedback to optimize movements (Jueptner, Jenkins et al. 1996). Our participants were dependent on only the kinetic and proprioceptive feedback from the legs and feet for treadmill belt speed changes, as visual feedback of the belts was blocked. Sensory feedback would then be relayed to the cerebellum, PPC, and SMA implement gait pattern changes. The cerebellum is an integration site for sensorimotor information from the spinal cord and cortex (Takakusaki 2013). The PPC uses sensory feedback to specify motor outputs for the upcoming steps and update an ongoing body schema (Gwin, Gramann et al. 2011, Drew and Marigold 2015, Hinton, Thiel et al. 2019). Finally, the supplementary motor area

will be active just prior to actual movement and aid in movement initiation planning (Fukuyama, Ouchi et al. 1997, Harada, Miyai et al. 2009, Hinton, Thiel et al. 2019). Under this model, this would explain why adults with PD can primarily use sensory feedback from the split belt treadmill to adjust the gait cycle, despite altered basal ganglia output, and show no large differences in gait symmetry performance compared to healthy older adults.

Study Limitations

Given that ^{18}F FDG uptake occurs over 30 minutes, this study was limited in this group of adults with PD who were required to walk independently off dopamine medication for 30 minutes without stopping and able to accommodate belt speed changes. In addition, this study was specific in its setup in order to comment on changes in brain activation (increase or decrease) during continuous adjustments to split belts based on the comparison to tied-belt walking to healthy older adults at the same age. Therefore, we cannot use the results presented here to comment on activity during typical walking on its own.

6.6 Conclusion

We propose that an over inhibition of the primary cortical motor networks from the basal ganglia due to Parkinson's disease results in compensatory cortical networks that are likely involved when complex locomotor planning and execution are required. All participants were able to adjust gait symmetry and time spent in stance and swing appropriately to the changes in belts speeds, however participants with PD required further activation or motor planning and sensorimotor activation areas. Based on these results, we hypothesize that an overdrive from the proprioceptive information from the feet and legs caused an excess in cortical resources required compared to healthy older adults, and potential compensation in fine motor control of the foot,

resulting in reduced foot angle at heel contact and toe off. This overdrive in cortical activation could also be contributing to the shuffling gait that is a hallmark of Parkinsonian gait. These cortical compensations were occurring at a relatively early stage of PD when gait impairments or freezing of gait did not impede participant's independence in day to day activities. It is therefore important to include these potential cortical compensations in the way we understand whole brain effects of PD beyond basal ganglia alterations.

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Chapter 7: General Discussion

7.1 Thesis Objectives

This doctoral thesis set out to further our understanding of the neural control of gait adjustment and adaptation to the split belt treadmill using three different methodologies: a systematic review of the literature, dual-tasking, and ^{18}F-FDG PET brain imaging. To reach our first objective, a systematic review of all relevant literature pertaining to the neural control of human gait adaptation to the split belt treadmill was completed (Chapter 3). Consolidating all current hypotheses for the human CNS' role in the split belt adaptation process led to the proposal of an overarching model of the split-bel treadmill adaptation process. This model included distinct roles for cortical and subcortical areas, cerebellum, and periphery (i.e. sensory feedback, CPG's) in the initial gait adjustments, gait adaptation and storage of the newly learned gait pattern. Given the recent "boom" in studies of human adaptation to the split belt treadmill, this work is important to ensure the literature maintains its focus on which areas of the human CNS are more important to this process of split belt treadmill adaptation. Work examining split belt treadmill walking has been primarily interested in "basic" science questions, including how the human CNS is able to walk on split belts, what changes occur to participants' gait pattern, and which clinical conditions are also able to maintain their walking pattern on the treadmill. However, there is also a broader interest in the possibility of using split belt treadmills as part of a physical rehabilitation program, that attempts to re-program the gait pattern. For instance, in a patient recovering from a stroke or dealing with effects of PD on the gait cycle, this treadmill has potential to be part of a neurologically based rehabilitation program. If these types of rehabilitation programs are going to be successful, a full understanding of which areas of the human CNS are imperative. Based on our

model proposed in Chapter 3, the cerebellum, and its communication with the primary motor areas, is of utmost importance for the storage of the newly learned walking pattern.

Next, the objective was to better understand the cognitive requirements of the split belt treadmill adaptation process using dual-task methodologies (Chapter 4). Compared to the imaging technique used later in the thesis, this approach is relatively simple to administer across a variety of populations. In addition, since a secondary task was used, to which the underlying neural control is already quite well understood, a more detailed hypothesis was made of the potential neural overlap between the *n-back* task and different aspects of the split belt adaptation process. In this experiment, it was found that the initial adjustment phase, when participants were first introduced to the split belts at different speeds, had the greatest effects on participants' accuracy to the n-back task. This finding did not align with the proposed model from Chapter 3, where it was hypothesized that the initial adjustment phase would likely be reliant on proprioceptive feedback to the spinal circuits and CPG's rather than higher order cognitive input. However, from our results in the dual task work, it became clear that when presented with both a challenging cognitive task and walking on split belts, young adult prioritized cognitive resources for their walking performance and a detriment to cognitive performance occurred. Discussion of this cognitive overlap is presented below.

Finally, the thesis identified the neural correlates of gait adjustments to the split belt treadmill healthy young adults (Chapter 5) and healthy older adults and adults with PD (Chapter 6) using PET neuroimaging. The investigations in these chapters compared split belt treadmill walking to typical treadmill walking to identify areas specific to complex locomotion and a *Fine-Tuning Network* for adjusting the gait cycle from one step to the next was proposed. Given the constraints of FDG PET imaging (i.e. uptake time of 30 minutes, requirements for continuous

walking), a walking task was created that continuously repeated the initial adjustment phase of the split belt treadmill adaptation protocol. By altering the speed ratio between belts every 15 (young adults) or 30 (older adults, adults with PD) seconds, it was not only observed how the gait pattern adjusted from one-step to the next, but also how the overall brain areas that were changing activation from typical walking. The implications of this network are discussed further below.

7.2 Finding the limits to cognitive resource allocation

While the details of the changes in brain activation from typical walking to continuous adjustments of the walking pattern have been discussed at length in Chapters 5 and 6, I would like to expand their comparison to the known brain networks underlying the *n-back* task (Chapter 4). Hopefully this discussion will allow for a better understanding for the specific areas that were active at the same time when I saw the detriments to *n-back* task accuracy in Chapter 4. Different executive functions activate or involve three distinct bilateral anatomical areas: the frontal pole (rostral PFC, Brodmann Area (BA) 10), the dorsolateral PFC (DLPFC, BA 9, 46) and the mid-ventrolateral (VLPFC, BA 45, 47). The mid-VLPFC is the first level of interaction of working memory, required for the n-back task, and it is in this area that active comparisons and judgements of stored information held in working memory are made (Petrides 1994, Petrides 1995, Owen, Evans et al. 1996, d'Esposito, Aguirre et al. 1998, Owen 2000). This area was not shown to increase activation during the continuous adjustment trial for young adults (Chapter 5), however an aspect of this area was shown to increased in adults with PD (Chapter 6; inferior frontal gyrus). While it is likely that the dual-task scenario in Chapter 4 did ask participants to increase activity in this area to properly complete the n-back task, this is likely not an area of conflict between tasks for young healthy adults.

The frontal pole (along with the DLPFC) has been implicated in the process of branching and integrating working memory with attentional resource allocation. This aids in keeping a main goal in mind (i.e. responding to a correct cue) while performing other sub-goals (i.e. altering the current cue held in memory), and being able to return to the task at hand (Koechlin, Basso et al. 1999). While the n-back task increases activity in this area, this area was one of the regions that decreased activity during the continuous adjustment trial compared to typical walking in healthy young adults. In addition, it was in this area that the decrease in activation was related to participants' variability where those who decreased this area the most also had the least variability from one step to the next (Chapter 5). This evidence suggests that participants in the dual task experiment who activated this area during the initial adjustment phase of the split belt adaptation may have also been those who had the greatest decrease in n-back task accuracy. In support of this hypothesis, this was an area that increased in activity during the continuous adjustment phase in adults with PD (Chapter 6). It appears that this area is likely an area that could cause conflict in cognitive resources when dual tasking during the initial adjustment phase of the split belt adaptation process.

Finally, it appears that sensorimotor integration areas are a likely candidate for cognitive resource allocation conflict during dual tasking split belt treadmill adaptation. The posterior parietal cortex (PPC) has been shown to be involved in the short term storage requirements used for decision making during a working memory task (Smith and Jonides 1998). Dorsal inferior PPC activation serves to focus attention on items within working memory whereas the ventral inferior PPC is responsible verbal and non verbal information distinctions, for encoding verbal information and phonological short term storage (Ravizza, Delgado et al. 2004). The PMC and SMA are involved in visuospatial attention maintenance during the delay between stimulus and response

(Jonides, Smith et al. 1993, Owen, McMillan et al. 2005) and the articulatory rehearsal process (Smith and Jonides 1998, Ravizza, Delgado et al. 2004) required during working memory tasks. These were also common areas of activation during the continuous adjustment trial for both young healthy adults and adults with PD (Chapters 5, 6). These areas are highly involved in sensorimotor integration during motor task performance and therefore are likely a large source of cognitive interference for the healthy young adults while dual tasking during the initial adjustment phase of the split belt treadmill process.

7.3 Implications of the *Fine-Tuning Network*

From this thesis work I have been able to inform our understanding of the neural control of complex walking adjustments from one step to the next. In the literature cited in this thesis, hypotheses for how the human CNS adjusts and adapts the gait pattern to the split belt treadmill was varied and widespread. In this thesis, I achieved my first objective of identifying, summarizing and comparing the current literature testing the human CNS on the split belt treadmill. From this review (Chapter 3), I was able to propose a model for how the CNS adjusts, adapts and stores a gait pattern for the split belt treadmill. This model brought together all the relevant research in the neural control of split belt treadmill walking and extends our understanding of brain activity during gait adaptation. Key to this model was the differentiation of the adaptation process (and its neural control) into three distinct time periods: adjustment, adaptation and storage. Understanding that the ability of the CNS to adjust and adapt the gait cycle appear to be using complementary, but different, neural mechanisms to achieve each of these goals, may help to further research into how to re-teach an injured CNS to achieve gait symmetry.

The understanding that neural control of gait *adjustment* may differ from gait *adaptation* was further supported by the results of the dual-tasking paradigm in Chapter 3. These results re-emphasized the importance of understanding the neural organization of each of these time phases. While unable to achieve the same specificity as PET imaging, our dual-tasking work provided further support of a change in the neural control underlying gait adjustments versus gait adaptation. After further, more specific, exploration of this adjustment phase with PET imaging, a *Fine-Tuning Network* of neural control for locomotor adjustments was proposed. This model is important to the understanding of the human CNS and its control of walking as it provides direct evidence of brain areas responsible for sensorimotor integration on a short-term time scale (i.e. from one step to the next). Previously, literature in this area has been reliant on animal models or superficial imaging methods (i.e. Functional near Infrared spectroscopy or electroencephalogram), likely during imagined walking. This model expands upon our understanding of steady-state locomotion and planned changes to the walking pattern to incorporate what we understand to be brain areas responsible to altering the gait pattern from one step to the next. These areas would be acting in an ongoing manner to create a "backup" for when the locomotor plan and its modifications are insufficient to maintain the walking pattern in the current environment. The model also provides new avenues for future work in the study of mobility and aging. The types of step-to-step changes studied in this thesis are potential sources of mobility limitations in healthy aging and the *Fine-Tuning Network* provides potential targets for future neurorehabilitation protocols to aid those with neurologically-based mobility challenges.

This model was then tested by expanding the imaging cohort to include healthy older adults and adults with PD. Imaging these populations allowed us to test our model in a scenario where cognitive resources are already being challenged either due to age or neurodegeneration.

Understanding how this model is used both in a young healthy CNS as well as one where cortical or subcortical resources are challenged, allows us to better understand how the CNS itself adapts to maintain locomotor performance. The research presented in Chapters 5 and 6 will be important to the growing discussion of how the human CNS adjusts and adapts brain networks to motor task requirements. For our young adult participants, this included further de-activation of the Default Mode Network (DMN) during continuous adjustment of the gait cycle. This de-activation demonstrated the ability of the CNS to provide a cognitive release and allow participants to rely more heavily on automatic, underlying, neural control networks. The same walking task in healthy older adults and adults with PD did not produce the same result. While they were able to adjust and adapt their gait cycle to the challenge of the continuous adjustment trial, they were unable to employ the same deactivation of the DMN. At this point, it must be reiterated that all participants *were* able to walk on the split belt treadmill without difficulty for 30 minutes, including adjusting their gait pattern on an ongoing basis. The human CNS adjusts and adapts its own resources to the task at hand so that the motor performance is appropriate for the environment. However, this is not without repercussion. We would hypothesize that if we were to challenge older adult participants with performing a secondary task during split belt treadmill adaptation, they would not be able to accommodate both at the same level as we observed in our healthy young adults. Given the wide network of cognitive resources required to incorporate the step-to-step adjustments on its own, the addition of a task that also requires cognitive resources from similar sensorimotor integration areas would cause a conflict in resource allocation.

7.4 Conclusion

This thesis contains some of the first work to suggest a specific model for the neural control of gait adjustments in a healthy human CNS and the changes that occur to this control with PD. To meet the thesis objectives, a systematic review of the current literature was conducted (Chapter 3), a dual-tasking methodology was assessed in healthy young adults (Chapter 4) and brain imaging was conducted in healthy young (Chapter 5) and healthy older adults and adults with PD (Chapter 6). This doctoral work provides a launching point on which to continue to understand how the human CNS controls an integral part of our day to day functioning. As we better understand both neurodegeneration and the brain networks that it affects, we can begin to understand how rehabilitation of certain facets of these networks will help those affected by the devastating effects of the loss of control of locomotion.

Chapter 8: Thesis References

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