EVALUATING MULTIMODAL BIOFEEDBACK TO TARGET AND IMPROVE MOTOR CONTROL IN CEREBRAL PALSY

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Abstract

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Early gait rehabilitation is a critical priority for individuals with cerebral palsy (CP), as neurologic injury in development alters motor control and can lead to a series of progressive impairments which may limit independent mobility. However, given the inherent heterogeneity of brain injury, developing strategies that can consistently improve function in CP has proven challenging; to date, outcomes from traditional interventions elicit measurable gait changes in approximately 50% of cases and often fail to directly target motor control. Biofeedback training, whereby individuals are provided with real-time information on gait performance, is a promising alternative to traditional interventions, as systems can be flexibly tuned to provide individualized and task-specific practice. Yet, early studies using biofeedback in CP have reported many of the same limitations as traditional interventions, outcomes are often unsatisfactory and motor control is largely unchanged. As such, in order for biofeedback systems to be reliably integrated into

clinical care, there is a need to understand and improve upon this heterogeneity. The goal of this dissertation is, therefore, two-fold: (1) to understand the factors that modulate motor control during gait which will help inform the extent to which it can be effectively targeted with biofeedback, and (2) to characterize how the design and implementation of biofeedback systems may influence outcomes.

In order to successfully alter motor control in individuals with CP using biofeedback, there is a need to first understand which factors may underlie such measures. Motor control following neurologic injury is simplified relative to nondisabled individuals, defined by greater co-activity of antagonist muscle groups during walking. While these simplified strategies are hypothesized to be the direct result of decreased involvement of supraspinal pathways in the production of movement, they may also partially reflect the biomechanical constraints imposed by pathologic gait patterns. To isolate the effects that altered gait has on motor control, we evaluated whether motor control strategies changed when nondisabled adults emulated common gait patterns in CP (*e.g.*, crouch gait, equinus). During emulation, motor control did not change significantly from baseline and did not align with motor control strategies observed in a cohort of individuals with CP walking in the same patterns. Together, this bolsters evidence that simplified motor control in CP is a direct effect of the primary neurologic injury and may, therefore, not be significantly improved by solely targeting gait kinematics via intervention.

The observed stability of motor control during gait pattern emulation aligns with prior studies which have demonstrated that motor control strategies are robust across changing biomechanical contexts such as cycling, running, and walking with partial body-weight support. Although collectively this suggests that motor control may be inflexible and, therefore, not modifiable with biofeedback training, this work has been largely constrained to a subset of

achievable walking configurations, limiting the overarching conclusions which can be drawn. As such, we evaluated the extent to which nondisabled adults could dynamically modify motor control using a custom-built motor control-based biofeedback system to guide broad gait pattern exploration. The resultant data set enabled us to model how motor control changed as a function of imposed biomechanical constraints. We found that individuals could consistently simplify motor control in response to biofeedback by altering their gait mechanics, predominantly at the knee and ankle. This work suggests that motor control *may* be modified during biofeedback training, but that the extent of that modification is contingent on the parameter targeted.

While the results of these studies ultimately improve understanding of the extent to which motor control may be modified during walking, other factors may influence response to biofeedback training that warrant additional investigation. In particular, although a variety of biofeedback systems have been developed for use in CP, it is unclear how the choice of modality used to communicate error may affect response. We compared how individuals with CP adapted motor control in response to audiovisual and sensorimotor biofeedback paradigms when administered independently and in combination; both systems were designed to directly target plantarflexor recruitment. We found that individuals were able to rapidly modify plantarflexor activity using each of the biofeedback paradigms, but that they primarily relied on the audiovisual system to guide movement correction. This indicates that individuals with CP may differentially prioritize distinct forms of biofeedback which must be considered in the future design of systems.

Individuals' capacity to retain improvements with repeated biofeedback training and transfer in-session gains beyond the training paradigm may also underlie the heterogeneity of outcomes. Extending experimental frameworks in motor adaptation, we evaluated how motor

control changed as a function of multi-session practice with audiovisual and sensorimotor biofeedback and whether changes were retained once biofeedback was removed. We observed that the extent to which individuals retained adapted gait patterns was contingent on the magnitude of in-session gains. This suggests that an individual's adaptation capacity may dictate their response to biofeedback and may, therefore, be valuable to consider when selecting optimal candidates for training.

Biofeedback training is an exciting avenue to personalize rehabilitation for individuals following neurologic injury and may serve as a non-invasive alternative to traditional interventions. By developing analytical frameworks to better understand motor control and evaluate how individual capacity and system design choices influence response to biofeedback, this dissertation lays the foundation to advance the design of clinically translatable systems which can support long-term, independent mobility in CP.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

INTRODUCTION

Independent mobility is critical for development and daily participation, as it enables individuals to interact with their peers, explore their environments, and engage in work, school, and recreation[1–4]. However, for individuals with cerebral palsy (CP), a neurologic injury at or near the time of birth adversely impacts motor control and may lead to a cascade of progressive musculoskeletal impairments including joint deformity, muscle contracture, and arthritis[5,6]. This means that while the majority of those with CP may be ambulatory in childhood, walking capacity can rapidly diminish by early adulthood, causing individuals to miss critical milestones and hindering independence in activities of daily living[7–9].

Given the importance of preserving mobility, most individuals with CP will undergo a slate of interventions in childhood which may include assistive device prescription and intensive physical therapy as well as highly invasive procedures such as regular botulinum toxin injections or orthopedic surgery[5,10]. Traditionally, such interventions are designed to directly target downstream musculoskeletal impairments with the ultimate goal of producing more 'normative' gait patterns. However, only about half yield meaningful improvements in walking and often impose a significant emotional and financial burden on both individuals and their caregivers[10–17]. Further, by failing to alter the underlying motor control strategies used in movement, many existing interventions serve only as stopgaps in CP care, requiring that individuals undergo multiple interventions throughout childhood to maintain walking function[15,18–20].

Due to the limitations of existing interventions, there has been urgent priority in CP rehabilitation placed on developing strategies that can be tailored to match the abilities and mobility goals of each individual and more directly target the primary neurologic injury.

Biofeedback training, in which individuals are presented with a real-time measure of gait performance, is one such strategy that has seen growing interest in the last ten years, aided, in part, by the improved accessibility and affordability of real-time monitoring[21]. Such systems may be particularly valuable for individualizing rehabilitation and prompting neuroplasticity following neurologic injury, as they facilitate task-specific and self-initiated movement practice[4,22–26]. In pilot studies, audiovisual, sensorimotor, and immersive biofeedback systems have been shown to elicit changes in gait mechanics, joint power, and walking economy in CP[21,22,27–33]. However, the field of biofeedback training in CP is still nascent and is, therefore, underscored by many of the same shortcomings as traditional interventions; responses are highly heterogeneous and training paradigms do not consistently prompt long-term changes in motor control[22,34].

Advancing the development of biofeedback systems requires that we first build a foundational understanding of existing outcome variability. The complexity of the neuromuscular system and the user-device interactions required for biofeedback training means that this variability is likely multifactorial, resulting from both individual capacity and system-level design choices. However, there has been limited attention thus far placed on understanding the contributions of each, highlighting an exciting avenue for continued research which may ultimately improve the viability of biofeedback as a clinical tool to promote long-term independent mobility in CP.

1.1 Focus of the dissertation

This dissertation aims to characterize how individuals interact with biofeedback and how both neurologic injury and system design influence responses. Specifically, I have focused on biofeedback systems designed to support walking function and improve motor control to inform the development of clinically translatable systems. As modifying motor control has thus far been

an elusive goal within CP rehabilitation[34,35], we aimed to first understand whether motor control can be modified during walking. In CP, motor control is simplified relative to nondisabled peers, which is hypothesized to reflect decreased reliance on supraspinal pathways and increased reliance on spinal circuitry to shape movement[36–38]. This may suggest that following neurologic injury, motor control may be inflexible and, therefore, more challenging to change, as implied by prior intervention outcomes [34,35]. However, there is still limited understanding of the factors which may contribute to simplified motor control in CP and the capacity for individuals to dynamically improve their motor control during gait. As such, starting with nondisabled adults, we designed two studies to address each of these gaps. In the first study, we evaluated the extent to which specific pathologic gait patterns that are commonly observed in CP, such as crouch gait and equinus (toe-walking), contribute to altered motor control (Chapter 3). By having nondisabled individuals emulate these gait patterns, rather than collect directly from individuals with CP, we were able to isolate the effects of altered gait mechanics. We found that individuals did not significantly modify their motor control strategies during emulation. This result indicates that simplified motor control in CP is not due to pathologic gait patterns alone and provides additional evidence for the general inflexibility of motor control during walking. But, as this study was limited to a small subset of achievable gait patterns, in our second study we aimed to understand if motor control was equally robust across a much larger array of patterns. To answer this question, we presented participants with motor control-based biofeedback to encourage broad gait pattern exploration and quantified if and how motor control changed as a function of altered biomechanical constraints (Chapter 4). We found that individuals could dynamically *simplify* motor control using biofeedback, aligning more closely with motor control strategies seen in CP. Further, these changes in motor control were largely driven by changes in distal gait mechanics, specifically

sagittal plane ankle and knee kinematics. Together, this suggests that motor control may be modulated during walking, but the extent of modulation is dependent on both the type and magnitude of imposed biomechanical constraints.

The outcomes from our first studies help to contextualize the reported rigidity of motor control and provide insight into how the central nervous system coordinates gait. However, because individuals were only able to simplify motor control during walking, they provide limited insight into the extent to which motor control may be improved in CP. As such, the second two studies of this dissertation were centered on understanding the extent to which biofeedback could consistently induce improvements in motor control in a CP cohort. Specifically, we were interested in characterizing how the design and implementation of biofeedback systems may influence response. For both studies, we developed and deployed audiovisual and sensorimotor biofeedback paradigms which were designed to target plantarflexor activity and have previously shown promise in improving motor control for children with CP[27,39,40]. Using these systems, we first compared how the choice of biofeedback modality impacted individuals' ability to modify gait and muscle activity (Chapter 5). The results from this study highlighted that audiovisual biofeedback may be particularly valuable for amplifying user response, as individuals adapted to a greater extent using this system as compared to the sensorimotor paradigm. Secondarily, we evaluated how response to biofeedback changed as a function of training to understand the capacity for individuals with CP to retain knowledge of a biofeedback environment and transfer in-session gains to improvements in walking performance (Chapter 6). We found that individuals consistently modified motor control across sessions and that retention of these modified patterns was contingent on the extent of in-session gains. This suggests that an individual's capacity to adapt gait patterns may be directly related to their outcomes following biofeedback training. Collectively, these

analyses provide a foundation to understand variable responses to biofeedback training and guide the development of novel systems that can be integrated into rehabilitation.

1.2 SIGNIFICANCE

This dissertation draws from the fields of mechanical engineering, biomechanics, neuroscience, and rehabilitation to improve the efficacy of biofeedback training in CP and, therefore, makes important contributions to each. By capitalizing on and combining robust analytical techniques in motor control, motor learning, and gait training, we can begin to untangle the complex and multifactorial response to biofeedback to inform future system design and expedite adoption into clinical care. As such, the primary contributions of this dissertation include:

Demonstrating that the biomechanical constraints of altered gait patterns do not explain changes in motor control in CP: Individuals with CP have simplified control strategies compared to nondisabled individuals[38,41]. However, there is still extensive debate as to the extent to which these strategies reflect and are affected by biomechanical constraints[42,43]. Using an emulation framework, we demonstrated that the biomechanical constraints imposed by common gait patterns in CP do not significantly affect motor control complexity. Specifically, nondisabled individuals walking in crouch gait and equinus (toe walking) exhibited different motor control strategies than a kinematically-matched CP cohort. This provides evidence that the simplified motor control strategies reported in CP reflect features of the underlying neurologic injury and are not solely a reflection of altered gait mechanics.

Characterizing how motor control strategies are altered to accommodate broad biomechanical constraints: There is a rich literature base that has quantified motor control in both nondisabled and clinical populations across distinct biomechanical contexts to better understand how the central nervous system coordinates diverse movement patterns[44,45]. While

there is a general consensus that motor control is robust to changes in task demand, existing studies have only evaluated a subset of movement patterns[46–48]. In this dissertation, we expand upon these studies by evaluating motor control across a much larger range of feasible gait patterns, which enabled us to more comprehensively understand how motor control changes as a function of imposed biomechanical constraints. Further, with these data we were able to capitalize on existing machine learning techniques to precisely evaluate the sensitivity of motor control to specific gait pattern changes; to our knowledge, this is the first study to implement this type of analytical approach to understand the neural control of movement.

Developing and evaluating the feasibility of a motor control-based biofeedback paradigm: Myriad biofeedback paradigms have been developed for use in both nondisabled and clinical populations to improve walking performance[22,49]. However, these systems have historically relied on single feedback metrics to guide movement correction such as ankle angle, joint power, or individual muscle activation timing[22]. As CP affects multi-muscle coordination, we aimed to understand the efficacy of presenting higher dimensional feedback to elicit more comprehensive changes in gait. To this end, we developed the first biofeedback system capable of quantifying motor control complexity during walking which enabled us to evaluate the capacity for individuals to comprehend high-dimensional biofeedback and modify motor control. This not only contributed to the field of biofeedback system design but provided a rich data set with which to improve our understanding of the plasticity of motor control strategies.

Comparing how the choice of biofeedback modality may differentially affect outcomes: Audio and visual biofeedback systems are frequently used in CP to guide movement correction, as both paradigms require minimal hardware to implement and are sufficiently flexible to target many different gait parameters[49]. We sought to understand if a trade-off exists between distinct

modalities of biofeedback to aid in the intentional design and selection of future systems. In the first study to compare response across unisensory and multisensory biofeedback modalities during walking in CP, we found that individuals relied heavily on audiovisual feedback, but that providing multisensory biofeedback elicited more rapid changes in gait.

Quantifying how individuals adapt gait patterns in response to biofeedback: Evaluating the capacity for individuals to adapt gait and retain in-session improvements during training may be critical to inform the development of biofeedback systems for CP. However, prior studies have been primarily limited to evaluating pre- and post-training outcomes, resulting in a trial-and-error style approach to biofeedback system design [21,22,34,39]. By extending techniques commonly used in motor learning literature, we were able to develop a more comprehensive understanding of how individuals learn to use biofeedback and how that response may change as a function of practice, fatigue, and biofeedback modality. While our findings primarily contribute to biofeedback training in CP, the experimental paradigms we employed can be easily extended to other populations and interventions.

1.3 Dissertation Overview

This dissertation includes four experimental studies, presented as self-contained articles, which are centered around characterizing and deploying biofeedback strategies that can reliably target motor control during gait. Chapter 2 provides an overview of relevant background material to provide context and facilitate interpretation of the subsequent chapters. Chapter 3 examines the extent to which the pathologic gait patterns commonly observed in CP alter motor control, to provide insight into the gait parameters which may be targeted to elicit improvements in motor control (Spomer, et al. *Journal of Biomechanics*, 2022). Chapter 4 then expands on this analysis to evaluate the extent to which motor control changes across a broader array of achievable gait patterns, to further

elucidate the relationship between biomechanical constraints imposed during walking and motor control (Spomer, et al. *Journal of Neurophysiology*, *In review*). Chapter 5 evaluates if and how user response changes when audiovisual and sensorimotor biofeedback systems are used independently and in combination to guide movement correction (Spomer et al., *In preparation*). And Chapter 6 characterizes how individuals learn to use sensorimotor and audiovisual biofeedback in parallel across a multi-session protocol to identify factors that may drive heterogeneous outcomes (Spomer et al., *In preparation*). Finally, Chapter 7 provides a summary of the contributions of this work and highlights critical directions for future research.

Chapter 2

BACKGROUND

2.1 CEREBRAL PALSY

Cerebral palsy (CP) describes a group of neuromuscular disorders resulting from an injury to the developing brain near the time of birth that primarily affects motor control[6,50]. Globally, CP has a prevalence of approximately 0.3% of live births, making it the most common cause of motor disability in childhood[51–55]. Of those diagnosed with CP, the majority walk independently (58.2%) or with a hand-held mobility aid (11.1%)[52]; however, walking is often challenging and may degrade over time due to disturbances in sensation[6,50], proprioception[56] and muscle tone[57,58] as well as the presence and progression of secondary musculoskeletal impairments[5,6]. Although the primary neurologic injury in CP is considered to be static, individuals may exhibit changes in bone morphology, muscle physiology, and muscle structure throughout their lifetime[5,6], resulting in energetically costly gait patterns[59–61] and increasing incidence of joint pain, injury, and fatigue[7,62–65]. Among those with CP, over a third report significant deterioration in walking ability by early adulthood, which adversely impacts independence in performing activities of daily living and participation in work and recreational activities[7–9].

As preserving independent mobility is important for promoting broad social, emotional, and cognitive development[1–4] and may alter the time course of secondary impairments[4,7,65,66], a broad array of intervention strategies have been developed to this end[10]. Commonly, individuals with CP perform physical therapy throughout childhood which may include strength training[11], serial casting[67], functional electrical stimulation[68], and treadmill training[69,70]. Ambulatory individuals are also often prescribed mobility aids such as walkers or ankle-foot orthoses (AFOs), the latter of which are designed to passively assist and resist torque about the ankle to improve gait

mechanics and energetics during walking[25–27]. Beyond non-invasive strategies, pharmaceutical approaches such as intramuscular botulinum toxin injections[71] and oral[72] and intrathecal[73] baclofen, are often prescribed to target increased muscle tone and spasticity (a velocity-dependent hyper-excitability of the stretch reflex[57]). Surgical interventions such as selective dorsal rhizotomy - a spasticity management procedure that involves cutting a fraction of the lower-limb afferent nerve fibers in the spinal cord - as well as muscle and tendon lengthening and rotational osteotomies - collectively termed multi-level orthopedic surgeries - are also regularly carried out in childhood[5,74]

Unfortunately, despite the abundance of intervention strategies, existing techniques are decidedly inconsistent, eliciting measurable improvements in gait in only about 50% of cases[10–17]. Further, because many available interventions are designed to address downstream impairments to produce 'normative' gait without eliciting changes higher up in the motor control hierarchy, outcomes are not commonly maintained long-term[34,35]. This often necessitates that individuals undergo multiple, often invasive, interventions to maintain mobility[15,18–20], which not only imposes a high emotional burden but results in lifetime medical expenses that are more than ten times those of non-disabled (ND) peers[75]. As such, developing intervention strategies that can *consistently* target and improve motor control impairments directly while simultaneously reducing patient burden will shape the future of clinical care in CP.

2.2 Motor Control

Characterizing how pediatric neurologic injury shapes motor control in CP is a critical first step in understanding altered movement patterns and establishing effective rehabilitation paradigms.

The neuromuscular system can generate a diverse array of coordinated movements through the precise integration of supraspinal motor centers (*i.e.*, cortex, basal ganglia, cerebellum, brainstem), spinal circuitry, sensory afferents, and the musculoskeletal system[76]. While this complexity ensures that humans can robustly navigate the complex and dynamic environments encountered daily, it also presents a daunting control problem; the inherent redundancy of the musculature creates an ill-posed scenario in which an abundance of equivalent motor solutions are available for any given task[77,78].

The strategies employed by the central nervous system to distill this deluge of neural signals and impose coordinated motor patterns are an ongoing topic of debate. However, it is hypothesized that central pattern-generating (CPG) elements within the spinal circuitry play a critical role in producing the rhythmic patterns observed in walking[79,80]. These elements are thought to couple the activation of groups of muscles which can then be flexibly combined to produce diverse motor outputs[78]. Not only does this architectural organization facilitate flexibility, but it serves to reduce the overall dimensionality of the system, therefore simplifying the motor control problem[77].

Evidence in favor of this theory was first presented using animal models, which demonstrated that in the absence of both supraspinal input and afferent information, rhythmic movement patterns could be generated via direct stimulation of the spinal cord[80–84]. While studies in humans have been less conclusive, seminal work in spinal cord injury populations have similarly demonstrated that electrical stimulation of the lumbar spine can elicit patterned locomotion-like movements[85,86]. Further, rhythmic stepping - characterized by wide, sinusoidal patterns of muscle activity - has been observed in newborns (0-8 months) well before the brain is fully mature and independent mobility has developed[36,37,87–89].

Although these studies suggest that spinal circuitry drives early human locomotion, reliance on these structures may change as a function of development. Maturation of the central nervous system results in increased involvement of supraspinal and sensory pathways in the control of movement[36,90] and simultaneous activity-dependent pruning in the spinal cord[87]. Greater supraspinal involvement not only enables more complex muscle recruitment but increases sensory integration, enabling faster and more robust adaptation to perturbation (See Section 2.4)[36,37,91]. Further supraspinal involvement helps regulate muscle tone, resulting in controlled inhibition of antagonistic muscle activation[5]. These changes correspond to the development of plantigrade gait, characterized by a prominent heel strike, smooth transition of the center of pressure, and narrower and more specifically timed muscle activation patterns (*i.e.*, at push-off, initial contact, swing)[36,37].

In contrast, in CP, neurologic damage in early development may adversely affect central nervous system maturation (Figure 2.1). While CP is a highly heterogeneous diagnosis and the primary injury can vary significantly in both size and location depending on the stage of development in which it occurs, the motor cortex is most commonly affected[92,93]. Damage to these supraspinal motor centers results in the delayed onset of movement[6], which can attenuate activity-dependent pruning within the spinal cord and decrease the overall connectivity between supraspinal centers, spinal circuitry, and sensory afferents[87,94]. Further damage to inhibitory projections may result in hyperreflexia, characterized by an increase in spasticity as well as greater co-contraction of antagonist muscle groups. Together, these changes may result in greater reliance on spinal circuitry to shape movement throughout development; this has been demonstrated in prior work, as individuals with CP retain the sinusoidal patterns characteristic of early development as they mature[37,94]. Aberrant muscle activity in early development will also

subsequently affect musculoskeletal development, leading to myriad sequelae which impact independent mobility.

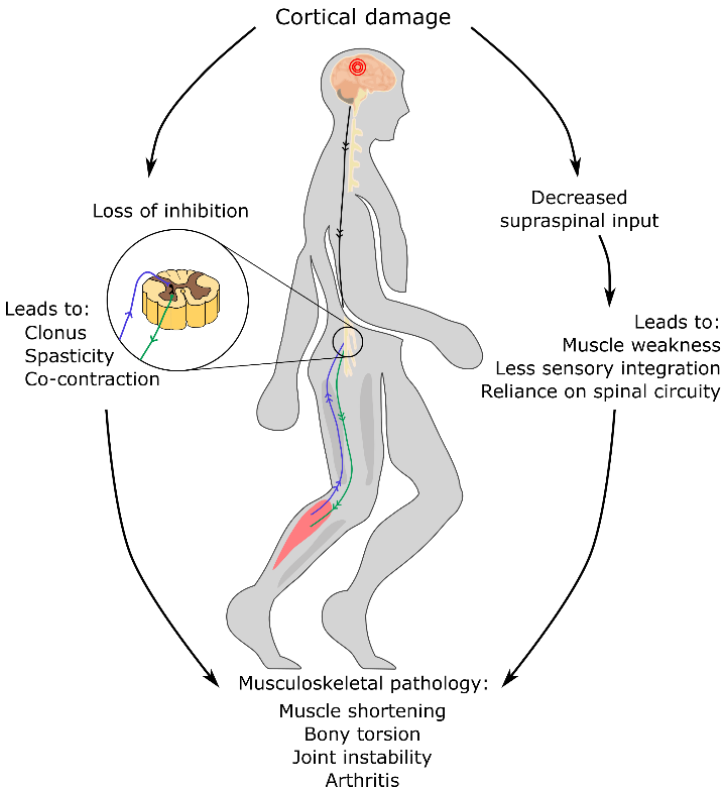

Figure 2.1 Overview of the effect that neurologic injury has on motor control in CP. Cortical damage in development leads to a loss of both inhibitory and excitatory descending signals which can manifest as hyperreflexia (e.g., clonus, spasticity) and continued reliance on spinal circuitry. Aberrant muscle activity may further alter musculoskeletal structure, leading to increased risk of injury and loss of independent mobility.

2.2.1 Quantifying motor control in CP

Given the implications that altered motor control has on long-term functional outcomes, a variety of strategies have been developed to directly quantify motor control in CP. In clinical settings, motor control is often characterized using assessment tools such as the Selective Control Assessment of the Lower Extremity (SCALE) and Gross Motor Function Measure (GMFM-66). The SCALE tool is used to rank joint-level control during a series of movements (*e.g.*, knee flexion/extension, ankle dorsiflexion/plantarflexion, toe flexion/extension) on an ordinal scale

from 0 (unable to perform the movement) to 2 (performs without ipsilateral or contralateral movement)[95]. In contrast, the GMFM-66 provides a more wholistic ordinal ranking of an individual's ability to independently initiate movement across five domains: (1) lying and rolling, (2) sitting, (3) crawling/kneeling, (4) standing, and (5) walking/running/jumping[96]. While each tool has high validity and interrater reliability and is sensitive to changes following intervention[95,97,98], neither provides a comprehensive picture of the control strategies which underly complex tasks.

As a supplement to traditional clinical assessment, electromyography (EMG) recordings have been broadly adopted in research to characterize muscle activity during movement. Most commonly, surface EMG sensors are used, which are affixed to the skin over the muscle belly and record the action potentials caused by depolarization and repolarization of motor units during muscle contraction[99]. While EMG enables rapid and noninvasive detection of the on/off firing of muscles, they are not without limitations; recordings can be noisy (requiring significant post-processing), time-consuming, require training to place correctly, and are sensitive to tissue characteristics, perspiration, body temperature and cross-talk with other muscles[99], all of which have slowed the adoption of EMG into clinical care[100]. However, unlike available clinical assessments, EMG signals provide a quantitative window directly into the central nervous system, making EMG a critical tool to begin untangling the complex interactions between neurologic injury and coordinated movement.

Although EMG is most frequently used to analyze how the activity (*i.e.,* timing, magnitude) of individual muscles changes within and between tasks, the development of analytical techniques such as muscle synergy analysis have made it exceedingly more valuable for quantifying multi-muscle control. Muscle synergy analysis capitalizes on existing matrix factorization techniques to

characterize the dimensionality of EMG data during a functional task[45]. Various linear techniques such as principal component analysis (PCA), independent component analysis, and factor analysis have been employed to this end, each of which presents a unique analytical advantage[101,102]; however, non-negative matrix factorization (NMF) is most frequently implemented[103]. NMF is used to decompose experimental EMG signals into a low dimensional subspace to identify weighted groups of muscles (W_{mxn}) - often called synergies, modes, or modules - and their corresponding activation coefficients (C_{nxt}), such that they satisfy the equation:

$$EMG_{mxt} = W_{mxn}\, x\, C_{nxt} + Error \qquad (2.1)$$

where m is the number of muscles, t is the number of time points, and n is the number of synergies (*i.e.*, components) used in the analysis. Unlike PCA, which creates a unique and orthonormal basis based on the variance in the original dataset, NMF identifies a non-negative basis using a search algorithm. As such, NMF not only requires that the number of synergies (*n*) is set *a priori*, but it means that the synergies identified are not optimal, and may, therefore, be slightly different between subsequent runs[101]. Despite these limitations, NMF is often seen as favorable for synergy analysis given its physiological applicability; the non-negative nature of the basis not only aligns more directly with neural output (in that neurons are either firing or at rest) but creates a 'parts-based' decomposition in which individual components can only be added to generate a movement pattern and means that each part is directly interpretable[101].

Muscle synergy analysis has become increasingly used to understand coordinated movement, as it is believed to provide an experimental correlate to the hypothesized architecture of the central nervous system; the muscle synergies extracted from NMF are theorized to reflect encoded elements that may be recruited by supraspinal and sensory pathways[43]. While the assumptions of NMF, specifically the linearity of individual synergies, may not align directly with

the global control strategy employed by the central nervous system (CNS), synergy analysis remains a convenient analytical tool to quantify how multi-muscle control changes with development and neurologic damage[42,45,104,105].

Using this technique, prior experimental and in-silico work has demonstrated that individuals recruit a basic set of synergies during walking that generally aligns with distinct subtasks: weight acceptance in early stance phase, push-off, toe clearance through swing, and limb deceleration in preparation for heel strike[46–48]. Further, this set of synergies remains consistent when individuals walk with altered mechanical demands (*e.g.*, changes in walking speed[46,106,107], cadence[108], incline[107], and gravitational loading[46,109]) and perform diverse tasks (*e.g.*, running[106], cycling[110], perturbation recovery[111,112]). The reported robustness of synergies across tasks with distinct biomechanical constraints is used as evidence that humans continue to rely, in part, on spinal circuitry beyond early development[113,114]; this is further supported by prior work which has demonstrated that the rhythmic stepping synergies in infancy are retained and combined with other emergent synergies to produce adult gait patterns[36,88]. However, interestingly, despite the relative invariance of synergy structures across varied movements, the temporal activation profiles are modified to accommodate task demand and, in instances in which movement patterns present 'distinct enough' afferent inflow, 'task-specific' synergies may emerge[113–116]. Taken together, these findings suggest that the increased supraspinal and afferent input resulting from the maturation of the CNS, facilitates greater precision in both the selection and combination of individual synergies, but that synergies remain centralized elements in the control of movement[114].

Synergy analysis techniques have also been extended to characterize how motor control changes as a function of neurologic injury. Prior studies have demonstrated that stroke survivors[108,117,118] and individuals with CP[38,41], spinal cord injury[119], and Parkinson's disease[120]

recruit synergies during walking that are less sparse (*i.e.*, have greater muscle coactivity) and less specific (*i.e.*, activated across the gait cycle) than synergies recruited by nondisabled peers. This has been hypothesized to directly reflect decreased reliance on supraspinal and afferent information to flexibly recruit synergies following neurologic injury[113,117]. The number of synergies recruited during movement has also been shown to change as a function of impairment level[38,108,118]. For example, in CP, recent research has demonstrated that synergy complexity is associated with functional measures of strength, selective motor control, walking speed, and spasticity whereby children with CP who exhibit less complex control during walking perform more poorly on functional measures[38]. Similarly, synergy complexity has been correlated to performance in mobility capability tasks (*e.g.*, maximum walking speed, maximum cadence, maximum step length, and maximum step height) among stroke survivors[108]. Synergies are also predictive of intervention outcomes; prior work in CP[121–123] and stroke[108] have demonstrated that individuals who have synergies more similar to nondisabled peers have greater improvements in gait mechanics following surgical intervention (CP) and treadmill training (stroke).

Collectively, these results suggest that synergy analysis is a clinically valuable tool to measure motor control and speaks to the potential efficacy of targeting synergies via intervention. Results from prior studies further suggest that developing strategies to alter synergies may not only improve function directly but, for those who still require surgical intervention, may positively affect post-operative outcomes[121]. There is evidence in nondisabled populations that synergies are differentially recruited with long-term athletic training[124,125] or during walking with ankle exoskeletons[126,127]. While emerging therapies (*e.g.*, spinal stimulation[128], exoskeletons[40]) have demonstrated promise to the same end, most traditional therapies in CP have minimal effect on

synergies[35]. As such, understanding if and how synergies can be consistently modulated in rehabilitation applications is a critical research area that motivated this dissertation.

Chapter 4 and Chapter 3 are centered around this question, as we aim to evaluate the extent to which synergies can be dynamically modified during walking as well as the factors which may contribute to altered synergies in CP.

2.3 BIOFEEDBACK

To develop strategies that can reliably target and improve motor control in CP, we can draw from a rich history of motor learning research. This prior literature suggests that for rehabilitation to effectively induce plasticity within the central nervous system, interventions must: (1) be *task-relevant,* (2) provide sufficient *challenge*, (3) encourage *active user engagement* and *motivation*, (4) facilitate *high repetition* and *high-intensity* practice, and (5) promote *reliable error feedback*[4,22–26]. Using these features as a framework, we can begin to understand the shortcomings of existing interventions and the opportunities for improvement. For example, treadmill training is commonly used in CP rehabilitation, as it provides task-specific and high-intensity walking practice[10,70,129]. However, for individuals to recognize and correct movement errors, they must rely on intrinsic (*i.e.*, tactile or kinesthetic) feedback pathways, which are often unreliable following neurologic injury, or therapist coaching, which may be insufficiently detailed or consistent to incite specific gait modifications[23,31,70]. In contrast, robotic gait training devices (*e.g.,* Lokomat) provide precise information on movement correction, often by guiding the limb through specific patterns[130]. Yet, this may simultaneously affect user engagement, as consistent guidance may reduce the need for intentional self-correction and make individuals more prone to 'slack'[131–133]. Together, these features likely contribute to the inconsistent and often unsatisfactory outcomes previously reported for both strategies[10,130]. However, when evaluating such interventions, it is

important to recognize that trade-offs will always exist, especially for a highly heterogeneous population such as CP. For example, robotic devices may offer a means of promoting more consistent practice for individuals that are not regularly ambulatory or are not able to support themselves while walking. Further, treadmill training offers the opportunity to extend gait rehabilitation outside of traditional clinical environments and provides more regular training opportunities. As such, there is a need to develop strategies that can preserve the positive aspects of individual therapies while simultaneously aligning them more closely with motor learning best practices.

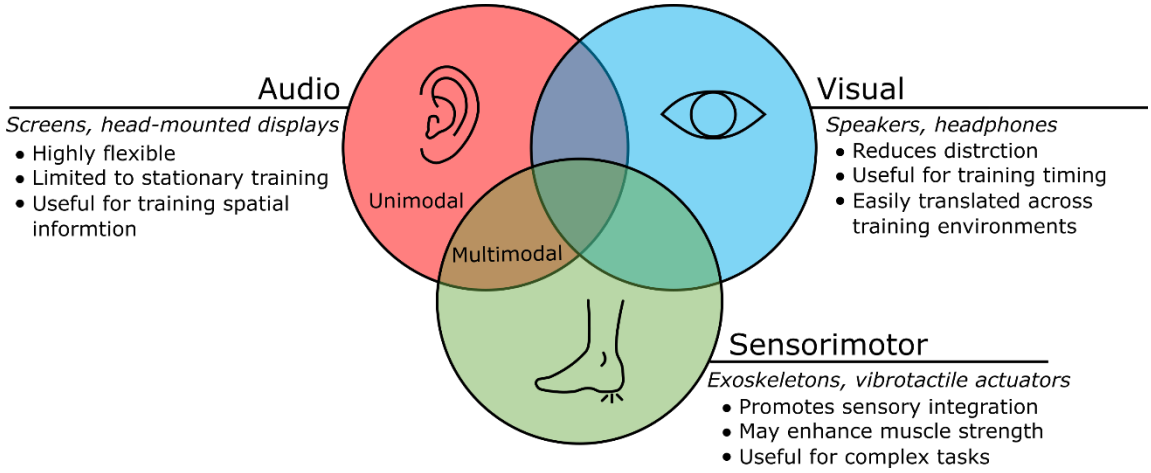

Figure 2.2 Biofeedback modalities commonly explored in cerebral palsy include audio, visual, and sensorimotor systems. Each modality has unique advantages that may make it better suited for specific gait training applications[134]. Biofeedback systems can also be administered independently (unimodal) or in combination (multimodal) depending on the population and target parameter.

Biofeedback is a promising means of augmenting existing gait training strategies, as it promotes self-initiated error correction and goal-directed practice[49,70,135–138]. Fundamentally, biofeedback systems are designed to provide a user with a measure of a specific parameter in relation to a desired performance, similar to traditional coaching strategies[22,138]. However, a unique advantage to these systems is that they offer a flexible platform, with many tunable parameters, that can be specifically tailored to match the therapeutic goals of the individual and adapt with

learning. These parameters may include: the method of presentation, the metric being presented, the frequency of feedback (*is the metric updated in real-time?),* the focus of attention (*are we prescribing specific joint angles or task-level goals?),* the timing of feedback (*is feedback being offered concurrently or at the end of the task?),* and the autonomy of feedback (*are individuals able to select if/when they want feedback?)*[22]. Each may affect the efficacy of biofeedback training overall and are, therefore, critical to understand. However, this dissertation will primarily be focused on understanding the effect of both the presentation method (*i.e.,* biofeedback modality) and metric on one's ability to modulate motor control.

Various biofeedback modalities may be used in gait training applications, each of which has specific advantages depending on the selected feedback metric and the target population (Figure 2.2). These include visual systems which communicate error information using screens or head-mounted displays, auditory systems, which use tones or music, and sensorimotor systems (*i.e.,* haptic systems), which use exoskeletons or vibrotactile arrays to provide tactile and proprioceptive information[49,134]. Each of these modalities has been previously used either independently (unimodal) or in combination (multimodal) to target a range of gait parameters among those with neuromuscular injury[49,139–143], although kinematic (36% of studies; *e.g.*, ankle, hip, and knee angles) and kinetic (35% of studies; *e.g.*, ground reaction forces, loading rate, ankle torque) feedback metrics are most frequently used[49].

In CP specifically, audio and visual feedback systems have been used to target and improve spatiotemporal parameters[29,31–33], muscle activity[29,144], and kinematics during walking[21,28–30] (Figure 2.3). More recently, Conner et al. demonstrated that training with a resistive ankle exoskeleton (hypothesized to provide sensorimotor feedback) elicited improvements in muscle strength[27], muscle activity[39], and walking efficiency[27] in a small CP cohort. The demonstrated

success of each of these modalities in CP points to the projected efficacy of integrating biofeedback into clinical care. However, in line with more traditional therapies, existing outcomes from biofeedback training in CP are still inconsistent and, even in the case of positive results, may not elicit lasting improvements in activities of daily living[22]. For example, a recent review by Macintosh et al. demonstrated that only 63% of parameters targeted by biofeedback in CP (*e.g.*, joint angles, EMG, applied force, etc.) were significantly improved following biofeedback training (Figure 2.3)[22].

As biofeedback training requires that individuals can effectively *recognize* movement error, response may be largely contingent on the modality selected for training. Both audio and visual systems are designed to provide extrinsic error information but do little to target faulty intrinsic signaling, which may impede robust error recognition and subsequent gait modification[56,145,146]. As such, pairing extrinsic systems with those which amplify intrinsic error pathways (*i.e.*, sensorimotor systems), may elicit a greater and more consistent training response than either paradigm alone. This is supported by prior work in nondisabled individuals[147,148] as well as in individuals following stroke[149] and spinal cord injury[139] which have demonstrated that presenting error information across multiple sensory pathways (*i.e.*, multimodally) elicits a faster and larger response than presenting information unimodally. Further, by combining multiple modalities of feedback, the advantages of each can be simultaneously exploited (Figure 2.2), enabling synchronous training of several different movement features (*i.e.*, timing, magnitude, movement path) without significantly increasing cognitive demand[134,150,151]; this may be particularly valuable for reinforcing complex tasks, such as walking.

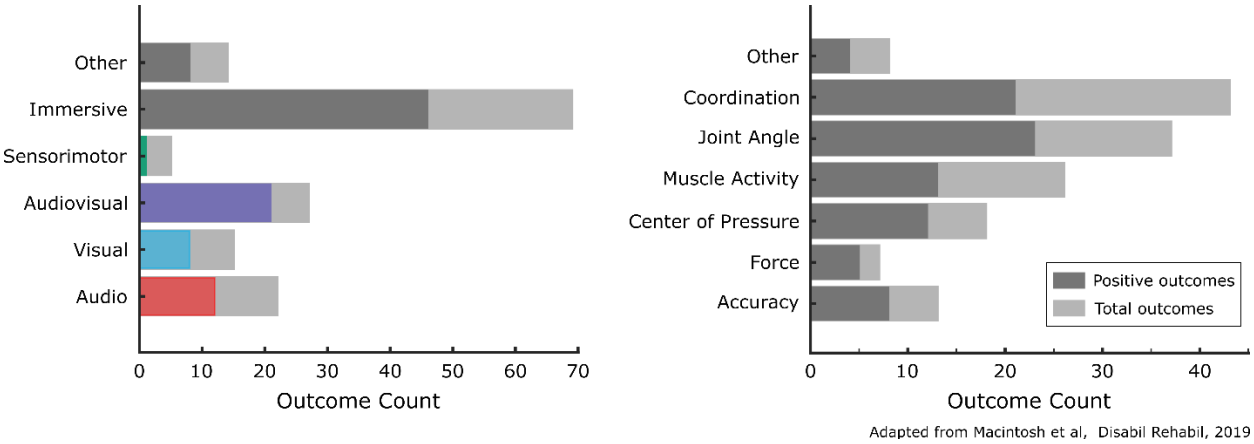

Figure 2.3 Overview of existing biofeedback studies in cerebral palsy, based on a recent review by Macintosh et al[22]. The left figure shows the distribution of different feedback modalities evaluated in CP and the right figure shows the different feedback metrics tested. In both plots, the light grey boxes depict the total number of outcomes tested and the darker grey and colored bars reflect the number of outcomes that were reported as significantly improved with biofeedback training.

Coupling sensorimotor and audio/visual systems may also be necessary to elicit longer-term changes in motor control in CP. In particular, providing precisely timed sensorimotor information in parallel with volitional movement enables us to effectively 'close the loop' within the central nervous system. This, in turn, may bolster supraspinal involvement in movement generation, resulting in greater inhibition of antagonist co-contraction and subsequent improvements in selective motor control[128]. A single pilot study in CP has so far provided evidence in support of this hypothesis. Recently, Conner et al. reported that multi-session training with sensorimotor biofeedback elicited a 5 ± 3% improvement in motor control complexity. Promisingly, all individuals within the small cohort (n = 5) demonstrated comparable changes in complexity, which represents a marked deviation from the success rate of both traditional interventions and biofeedback therapies[40].

The outcomes from prior studies lend credence to the value of using audiovisual and sensorimotor systems in CP and highlight the potential additive advantage of combining modalities

to further amplify responses. However, additional work is needed to evaluate how response differs between paradigms during walking.

2.4 Motor adaptation and learning

Beyond being able to *recognize* movement errors, individuals must be able to *adapt* their gait patterns in response to feedback and *retain* improvements with repeated exposure for biofeedback training to be successful. This suggests that not only is there a need to characterize how the choice of biofeedback modality influences response, but to simultaneously understand adaptation capacity within the context of biofeedback training and how it may be affected following neurologic injury.

Motor adaptation is defined as a process through which a well-learned movement pattern is modified by trial and error to accommodate novel perturbation[152]. This ability grants the nervous system a high degree of flexibility to account for changing task demand[152,153]. Experimentally, motor adaptation is characterized by systematically introducing and removing an external perturbation and measuring an individual's response. Using this framework, adaptation to a broad array of perturbations has been previously evaluated in reaching[154–158], walking[112,153,159–167], and balance[168–170]. In walking specifically, both single-leg weighting and split-belt treadmills are commonly used to impose unilateral or bilateral perturbations, respectively; the latter is accomplished by simultaneously driving each treadmill belt at a different speed[159]. Both paradigms have been investigated in nondisabled individuals and individuals with neuromuscular disorders, providing insight into how the unimpaired central nervous system modifies gait in response to perturbation and how neurologic damage influences this ability[159,161–163,166,171,172]. Adaptation to both perturbations is generally understood to be composed of two underlying processes that engage distinct areas of the brain: (1) a fast, feedback-driven response (*i.e.*, at the level of the spinal

circuits) at the onset of perturbation, used to ensure maintenance of forward walking and (2) a slow, feed-forward response (driven by supraspinal centers) as the individual modifies their gait to accommodate the perturbation and returns to baseline[173] (Figure 2.4). Following adaptation, removal of the perturbation results in an after-effect, characterized by an overcorrection in the adapted parameter followed by a gradual return to baseline (*i.e.*, washout); this has been hypothesized as evidence that the CNS has temporarily stored the perturbed gait pattern[152,164]. Further, with repeated exposure to the perturbation, adaptation typically occurs more quickly, indicating that the CNS has partially retained the adapted gait pattern to accommodate the novel environment[157,174].

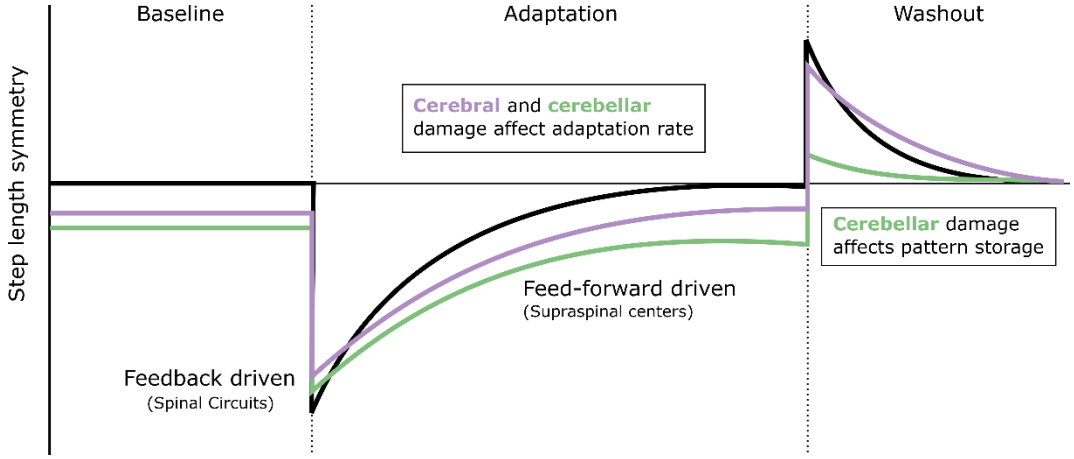

Figure 2.4 Expected response to split-belt treadmill perturbation among nondisabled adults (black) and individuals with cerebral (purple) and cerebellar damage (green) using a representative gait parameter (step length symmetry). Response to perturbation is mediated by multiple sites within the central nervous system.

Since adaptation is hypothesized to involve multiple brain centers, adaptation capacity is differently affected among those with neuromuscular disorders depending on the extent of the injury. In nondisabled adults, adaptation to both spilt-belt treadmill and single-leg weighting paradigms typically occurs over a 10-15 minute window[160,160,167,175,176]. In contrast, individuals with cerebellar damage often adapt more slowly and incompletely, meaning that they do fully

return to baseline during the adaptation period[177–179], but still demonstrate rapid correction in response to perturbation onset, suggesting that feedback pathways are preserved. Further, following perturbation removal, individuals demonstrate minimal after-effects, indicating that the adapted gait pattern has not been fully stored[177,180]; these findings have been used to confirm the role that the cerebellum plays in the feed-forward generation and storage of gait patterns. Similar observations are found among those with cerebral damage due to stroke[153,174,181–183], traumatic brain injury[184], and hemispherectomy[165], although after-effects align more closely with nondisabled adults. Interestingly, adaptation capacity in these populations has also been related to the way perturbation is presented. For example, prior work in stroke demonstrates that individuals will adapt more slowly and to a lesser extent if the imposed perturbation reduces baseline asymmetry rather than accentuates it[182]. This is used as evidence for the critical role that appropriate error detection plays in accelerating adaptation[182,185].

Adaptation among those with CP is thought to align with findings from other populations with cerebral damage. For example, prior work evaluating adaptation to single-leg weighting has indicated that children with hemiplegic CP can adapt intralimb gait kinematics and spatiotemporal parameters in response to perturbation, but demonstrate a smaller after-effect following perturbation removal compared to nondisabled peers[161,162]; these studies also secondarily confirmed that error augmentation (*i.e.*, weighting the more-affected limb) resulted in the greatest return to symmetry[161]. Similar observations have been made in split-belt treadmill paradigms, as Mawase et al. reported that individuals with CP adapt more slowly than nondisabled peers to perturbation, but that adaptation rate increases with repeated exposure and is maintained following a six-month washout[186]. Collectively, these results suggest that the ability to adapt gait and retain improvements is preserved among those with CP. However, studies are still limited [4,162,186] and

have been primarily focused on individuals with unilateral (*i.e.*, hemiplegic) involvement, which only represent a subset of the population; only a single study has evaluated adaptation among those with diplegic CP[186].

Beyond the need for greater understanding of how individuals with CP adapt to perturbation is the need to understand adaptation in the context of rehabilitation. While foundational adaptation studies can provide the scientific underpinnings of perturbation response, there is no evidence to suggest that these measures of adaptation in CP extend to common rehabilitation strategies such as biofeedback; this is supported by prior work which has hypothesized that adaptation may be specific to both the perturbation and context in which it is applied[112,162,163,167,187–190]. Similarly, because the rate of adaptation is dependent on an individual's ability to recognize movement error[191,192], it is likely sensitive to biofeedback system design.

As such, the aim of Chapter 5 and Chapter 6 is to evaluate biofeedback training through the lens of motor adaptation to understand how individual capacity and system design choices may underlie variable responses between individuals. This approach represents a marked deviation from both fields. Commonly, rehabilitation interventions are designed to target specific gait parameters and evaluated based on training outcomes alone, resulting in a 'trial and error' style approach to intervention design. Further, existing motor adaptation studies are confined to rigid experimental design and may not sufficiently capture the realities of gait training, limiting the translation of these findings. By drawing these fields together, we aim to contribute significantly to both; we can advance basic understanding of how adaptation may be affected following neurologic injury and simultaneously inform biofeedback system design to best amplify this capacity. Together, we believe that the outcomes from this work will improve the efficacy of

biofeedback as a non-invasive treatment option in CP and, ultimately, reduce the burden of care on both patients and their families.

Chapter 3

SYNERGIES ARE MINIMALLY AFFECTED DURING EMULATION OF CEREBRAL PALSY GAIT PATTERNS

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ABSTRACT

Muscle synergy analysis is commonly used to characterize motor control during dynamic tasks like walking. For clinical populations, such as children with cerebral palsy (CP), synergies are altered compared to nondisabled (ND) peers and have been associated with both function and treatment outcomes. However, the factors that contribute to altered synergies remain unclear. In particular, the extent to which synergies reflect altered biomechanics (*e.g.,* changes in gait) or underlying neurologic injury is debated. To evaluate the effect that altered biomechanics have on synergies, we compared synergy complexity and structure while ND individuals (n = 14) emulated four common CP gait patterns (equinus, equinus-crouch, mild-crouch, and moderate crouch). Secondarily, we compared the similarity of ND synergies during emulation to synergies from a retrospective cohort of individuals with CP walking in similar gait patterns (n = 28 per pattern). During emulation, ND individuals recruited similar synergies as baseline walking. However, pattern-specific deviations in synergy activations and complexity emerged. In particular, equinus gait altered plantarflexor activation timing and reduced synergy complexity. Importantly, ND synergies during emulation were distinct from those observed in CP for all gait patterns. These results suggest that altered gait patterns are not primarily driving the changes in synergies observed in CP, highlighting the value of using synergies as a tool to capture patient-specific differences in motor control. However, they also highlight the sensitivity of both synergy activations and complexity to altered biomechanics, which should be considered when using these measures in clinical care.

3.1 INTRODUCTION

For individuals with cerebral palsy (CP), neurologic injury near birth alters motor control, often making walking challenging and inefficient[5,59]. As such, many individuals will undergo surgical interventions to improve mobility. Yet treatment outcomes are variable and often unsatisfactory[12,13,193].

To improve the consistency of outcomes, recent research has investigated methods, such as synergy analysis, to directly characterize impaired motor control in CP[44]. Synergy analysis identifies weighted groups of co-activating muscles (*i.e.*, synergies, modes, or modules) from electromyography (EMG) data collected during movement[103,194]. Prior work has demonstrated that nondisabled (ND) adults recruit a small number of synergies during walking[46], running[195], and balance tasks[114,196]. In contrast, individuals with CP use fewer synergies during gait, similar to stroke survivors[117] or individuals with spinal cord injury[119] or Parkinson's disease[120]. Further, more impaired synergies are associated with worse function and treatment outcomes[35,41,121]. While these results highlight the efficacy of using synergies as a measure of motor control, it is unclear what factors contribute to altered synergies in CP.

Given the complex presentation of CP, many factors could impact synergies. Because CP affects the motor cortex, altered synergies may reflect atypical neurophysiology. This stems from work that suggests that stepping in early development is driven by spinal circuits (*e.g.*, central pattern generators) but becomes increasingly shaped by supraspinal pathways during central nervous system maturation[37]. Under this hypothesis, aberrant supraspinal input due to neurologic injury may increase reliance on spinal circuits, resulting in simplified control[43]. This is supported by work which has demonstrated that individuals with CP and spinal cord injury, as well as stroke survivors, use similar synergies to those observed during rhythmic-stepping in infants[36,117,119,195].

However, biomechanical constraints may also affect synergies. Individuals with CP adopt altered gait patterns, often characterized by toe-walking (equinus) and excessive knee and hip flexion (crouch)[61]. These patterns may restrict joint ranges of motion, effectively reducing the feasible activation space for muscles and contributing to altered synergies[42,197].

Analyzing how biomechanical and neurological constraints impact synergies in CP will inform the clinical use of synergy analysis. However, because these constraints are intricately coupled following neurologic injury, evaluating their contributions in CP directly is challenging. Alternatively, ND emulation of CP gait patterns presents a useful experimental paradigm to understand the effect of biomechanical constraints on synergies. Prior studies have used emulation to probe how CP gait impacts kinetics[198,199], metabolics[199], muscle activity[198–200], and muscle length[201]. While many of these studies noted altered muscle activations during emulation, whether synergies are affected remains unknown.

The purpose of this study was to evaluate whether synergies during ND emulation of CP gait (1) differed from those used during baseline walking and (2) aligned with synergies recruited by individuals with CP walking in similar gait patterns. We hypothesized that ND individuals would use similar synergies during baseline and emulated gait and that these synergies would be more complex than synergies used by individuals with CP. If supported, this hypothesis would suggest that altered synergies in CP reflect neurological rather than biomechanical constraints. This investigation will help identify the factors captured by synergy-based measures to inform the efficacy of using synergy analysis to guide treatment in CP.

3.2 METHODS

3.2.1 Experimental protocol

We recruited fourteen ND adults (7M/7F; median [IQR]: 23 years [21,25]) to analyze synergies during CP gait pattern emulation. All participants provided written consent and procedures were approved by the Institutional Review Board at the University of Washington.

Participants walked on a treadmill at self-selected speed (1.05 m/s [1.0,1.1]; Bertec Corp., Columbus, USA) while performing one three-minute baseline trial followed by three, three-minute trials in the following patterns: equinus (Eq), equinus-crouch (Eq-Cr), mild crouch (Mi-Cr), and moderate crouch (Mod-Cr). These patterns were selected as they represent approximately 69% (crouch) and 61% (equinus) of ambulatory children with CP[61].

Verbal instructions and visual cues were used to guide emulation. To emulate equinus, participants were instructed to maintain ankle plantarflexion through stance while minimizing knee flexion. For mild and moderate crouch, 20° and 30° of knee flexion were measured, respectively, using a goniometer during stance and reinforced in-trial with a hanging marker[202]. Participants were instructed to keep the marker at eye-level by maintaining knee flexion and minimizing trunk flexion[201]. To emulate equinus-crouch, participants adopted the same equinus posture along with 20° of knee flexion, set and reinforced using the same protocol as crouch.

Full-body motion data were collected using a modified Helen-Hayes marker set and a 10-camera motion capture system at 120 Hz (Qualisys AB, Gothenburg, SE). Joint angles were computed from marker trajectories in OpenSim v3.3 (Stanford, USA) using a 33 degree-of-freedom model scaled to each subject[203,204]. Across trials, the root-mean-square (RMS) and maximum model error for all markers were 1.4 cm and 2.5 cm, respectively, which align with best practices for model quality[205].

Surface EMG data (Delsys Inc, Natick, MA) were collected bilaterally for the gluteus maximus (GMAX), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), soleus (SOL), tibialis anterior (TA), and medial gastrocnemius (GAS). Raw EMG signals were high pass filtered (4th order Butterworth; 20 Hz), rectified, low pass-filtered (4th order Butterworth; 10 Hz), and normalized to the 95th percentile of maximum activation across trials[206,207]. Any data spikes due to sensor movement were removed using a robust-PCA algorithm[208,209].

3.2.2 Synergy analysis

Synergies were calculated using non-negative matrix factorization (NMF; Lee, 1999). NMF models EMG data as a linear combination of non-negative, time-invariant synergies (W) and their activation patterns (C) such that:

$$EMG = W_{mxn} * C_{nxt} + error \quad (3.1)$$

where *m* is the number of muscles, *n* is the number of synergies, and *t* is the number of time points. For each gait pattern, *n* = 1 to 7 synergies were calculated using dominant-leg EMG data. Because synergy analysis is sensitive to the amount of EMG data used, the same number of strides (n = 43) were analyzed across gait patterns and participants[210]. For the emulated gait patterns, these data were taken from the middle of the final trial to minimize learning effects due to pattern novelty. The structure and complexity of the resultant synergies were then compared across gait patterns.

3.2.3 Synergy complexity

We quantified synergy complexity as the total variance accounted for (tVAF) in the EMG data by a set of synergies (*n*), defined as:

$$tVAF_n = \left(\frac{1 - \sum_j^t \sum_i^m ((W_n * C_n)_{i,j} - EMG_{i,j})^2}{\sum_j^t \sum_i^m \left(EMG_{i,j}\right)^2} \right) * \ 100\% \qquad (3.2)$$

Here, a lower tVAF indicates that a set of synergies captures less variance in the EMG data, suggesting more complex motor control. Importantly, tVAF is associated with impairment level, as children with CP have higher tVAF than ND[38,41,121]. If altered gait patterns influence tVAF in CP, we would expect higher tVAF during ND emulation than baseline gait.

3.2.4 Synergy structure

To evaluate whether synergy structure changed during emulation, we first identified synergy weights (W) and activations (C) that were shared across patterns using k-means cluster analysis[211]. For each synergy solution, *n,* weights from all participants and gait patterns were sorted into *k* clusters in Matlab (MathWorks, Natick, USA). To allow for the possibility that pattern-specific synergies may emerge*,* clustering was performed with *k* ranging from *k* = *n* (*i.e.*, baseline and emulated gait patterns shared a set of synergies) to *k* = 5**n* (*i.e.,* all gait patterns had unique synergies). We selected *k* as the number of clusters with the maximum silhouette coefficient[212]. Median weights and activations for each gait pattern were then calculated from the resultant clusters.

We quantified the similarity of the synergy structures recruited during baseline and emulated gait by calculating how much of the variance in the emulated gait EMG data could be explained by baseline synergy weights ($W_{baseline}$). We used the multiplicative update rule from NMF to iteratively solve for C for each emulated pattern ($C_{emulation}$) while keeping $W_{baseline}$ constant. For each synergy solution, *n*, the reconstructed total variance accounted for ($tVAF_{n\_recon}$) was calculated using $W_{baseline}$ and $C_{emulation}$ (Equation(3.1) and compared to the original tVAF; if

synergy structure was similar during baseline and emulated gait, we would expect both tVAF values to also be similar.

3.2.5 Comparison to CP

Synergy structure and complexity during emulated gait were also compared directly to CP synergies using retrospective, overground walking data collected at Gillette Children's Specialty Healthcare. Two individuals with CP were matched to every ND individual for each emulated gait pattern. Individuals with CP were included in the matching pool if they had diplegia and walked without an assistive device, regardless of intervention history or injury severity. Matches were identified as those individuals with the smallest total RMS difference in sagittal-plane hip, knee, and ankle kinematics. To increase the diversity of our CP cohort, matches were selected without replacement, resulting in 28 unique individuals for each pattern (median age [IQR]; Eq: 11.1 [7.5,15.5], Eq-Cr: 10.6 [7.5,13.3], Mi-Cr: 12.5 [9.4,15.9], Mod- Cr: 12.1 [8.6,13.7]). Across all matches, the median cosine similarity was 0.94 [0.90,0.97], 0.98 [0.97,0.99], and 0.89 [0.77,0.95] and the median RMS difference was 13.7° [9.6,20.1], 9.0° [6.6,12.4], and 7.1° [5.2,10.0] at the hip, knee, and ankle, respectively. Dimensionless walking speed was also similar between ND and CP cohorts (Mann- Whitney U test; $p > 0.42$)[213].

For the CP cohort, we processed kinematic and EMG data (vastus lateralis (VL), MH, TA, GAS) using the procedures outlined above and performed synergy analysis for $n = 1–4$ synergies using three concatenated strides. For individuals with more than three recorded strides, we performed a bootstrapping procedure by calculating synergies from three random strides in the available set and replicating the process until a normal distribution was achieved. Average synergy weights and activations from the resultant distribution were then used to represent the individual's recorded data. We also recalculated ND synergies for the reduced muscle set and three

concatenated strides using the same bootstrapping procedure; however, VM was used in place of VL, as the latter was not collected experimentally. In both cohorts, k-means clustering was used to calculate median weights and activations for each gait pattern.

3.2.6 Statistical analysis

To evaluate if synergy complexity and structure changed between baseline and emulated gait patterns, Wilcoxon signed-rank tests were used with a Holm-Šídák correction for multiple comparisons (n = 4); non-parametric statistics were selected due to the small sample size [214]. Significant deviations in kinematics and integrated EMG between emulated and baseline walking were also identified using Wilcoxon signed-rank tests with correction for multiple comparisons. Further, Mann-Whitney U tests were used to compare synergy complexity between ND and CP cohorts for all synergy solutions (n). For all tests, we define significance as $p < \alpha$ for $\alpha = 0.05$ and report medians [IQR] unless otherwise noted. All statistical analyses were performed using the Matlab Statistical Toolbox.

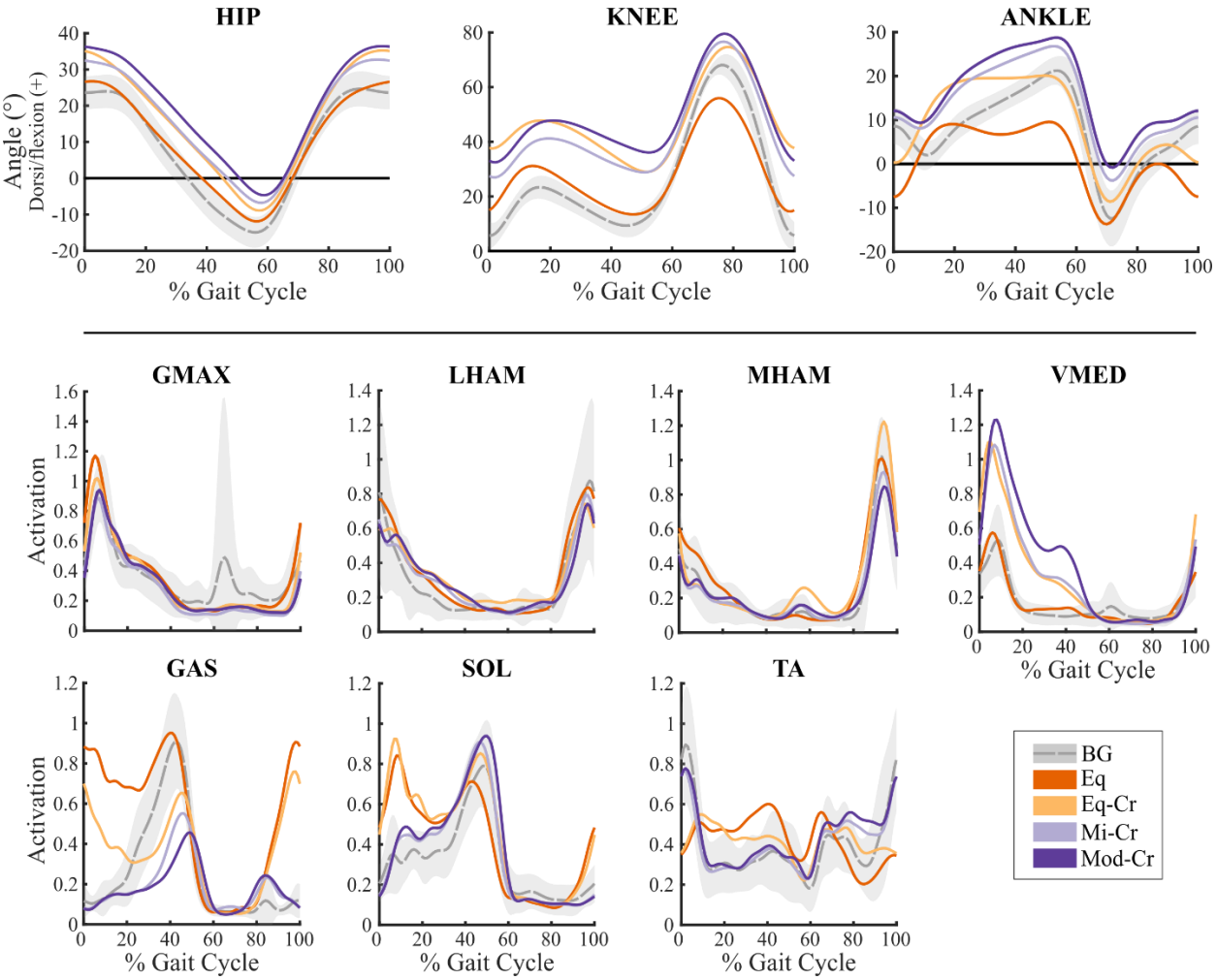

Figure 3.1 Median sagittal-plane kinematics (Top) and EMG (Bottom) during baseline, equinus (Eq), equinus-crouch (Eq-Cr), mild crouch (Mi-Cr), and moderate crouch (Mod-Cr) gait by ND adults. Shading indicates the IQR for baseline gait. Muscles: gluteus maximus (GMAX), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), medial gastrocnemius (GAS), soleus (SOL), and tibialis anterior (TA).

3.3 RESULTS

All participants emulated the major kinematic trends seen in equinus, equinus-crouch, mild crouch, and moderate crouch gait (Figure 3.1). In equinus, participants increased plantarflexion during weight acceptance (-6.85° [-9.8, -1.4]) and terminal swing (-2.2° [-9.4, -0.1]) and decreased dorsiflexion through stance compared to baseline ($p < 0.001$; Table 3.1). This corresponded to increased co-contraction of antagonists at the ankle at midstance ($p < 0.02$). Mild and moderate crouch were characterized by increased hip flexion, knee flexion, and ankle dorsiflexion in stance,

which corresponded to increased quadricep activity and reduced gastrocnemius activity ($p < 0.002$). In equinus-crouch, knee and hip flexion increased through stance and ankle dorsiflexion decreased at weight acceptance (0.02° [-3.0, 3.5]; $p < 0.02$). These changes were associated with increased quadricep and soleus activity through stance and increased gastrocnemius activity at weight acceptance ($p < 0.001$).

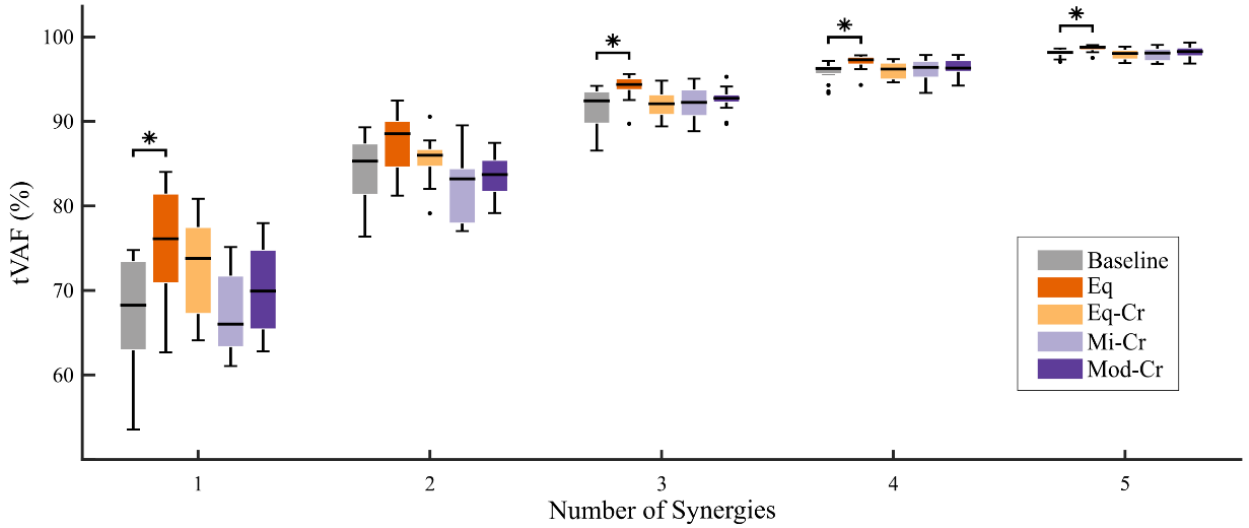

*Figure 3.2 The total variance accounted for (tVAF) by n = 1 to 5 synergies for baseline gait and each emulated gait pattern. An increase in tVAF corresponds to a decrease in control complexity. * denotes significant difference from baseline gait ($\alpha = 0.05$) using Wilcoxon signed-rank tests with a Holm-Šídák correction for multiple comparisons and dots indicate outliers. Gait patterns: baseline, equinus (Eq), equinus-crouch (Eq-Cr), mild crouch (Mi-Cr), and moderate crouch (Mod-Cr)*

Table 3.1 Sagittal plane kinematics of ND adults during baseline and emulated gait patterns.

	Baseline	Equinus		Equinus Crouch		Mild Crouch		Moderate Crouch	
Gait Variable (deg)	Median [IQR]	Median [IQR]	*p*	Median [IQR]	*p*	Median [IQR]	*p*	Median [IQR]	*p*
Hip									
Max extension	14.7 [11.6,17.9]	15.1 [8.3,18.4]	0.63	10.5 [8.0,12.9]	0.051	9.3 [6.8,10.4]	0.002*	5.7 [1.4,10.4]	0.002*
Max flexion	25.7 [20.9, 30.0]	26.4 [24.1,32.9]	0.30	34.9 [32.4,41.6]	< 0.001*	33.3 [32.0,38.9]	< 0.001*	37.9 [33.2,40.9]	< 0.001*
Knee									
Mean flexion in stance	19.4 [16.4,20.8]	21.3 [20.0,24.0]	0.02*	37.6 [35.7,45.8]	< 0.001*	37.8 [35.0,40.7]	< 0.001*	42.2 [39.0,47.7]	< 0.001*
Ankle									
Max dorsiflexion	21.4 [19.7,25.5]	10.5 [8.6,15.5]	<0.001*	22.2 [17.6,26.8]	0.98	28.2 [25.4,29.7]	< 0.001*	30.5 [29.1,30.9]	< 0.001*
Mean dorsiflexion in stance	10.4 [9.7,12.9]	4.3 [2.2,8.2]	< 0.001*	11.6 [10.7,18.5]	0.051	17.0 [14.8,19.8]	< 0.001*	19.0 [17.7,23.2]	< 0.001*

*Significant difference ($\alpha < 0.05$) from baseline using Wilcoxon signed-rank test with Holm-Šídák correction

3.3.1 Synergy complexity

The tVAF significantly increased during equinus gait for all synergy solutions except $n = 2$ ($p = 0.07$; Figure 3.2). However, in all other gait patterns tVAF was similar to baseline for all synergy solutions ($p > 0.09$). At baseline, one synergy accounted for 68.2% [63.0,73.4] of the variance in the EMG data compared to 76.1% [70.9,81.4], 73.8% [67.3,77.4], 66.0% [63.3,71.7], and 70.0% [65.5,74.8] for Eq, Eq-Cr, Mi-Cr, and Mod-Cr walking, respectively.

3.3.2 Synergy structure

Synergy weights were also minimally affected during emulation. The three-synergy solution was compared across patterns, which accounted for over 90% of the variance in muscle activity for most participants (Figure 3.3). Although *k* could vary, three clusters emerged across all gait patterns that were dominated by the gluteus maximus and quadriceps (W_1), the hamstrings (W_2), and the plantarflexors (W_3), similar to prior findings in ND adults[47,117].

Although emulated and baseline synergy weights were similar, differences in activations emerged. Equinus resulted in increased activation of W_3 through stance and terminal swing (C_3); the latter trend has been reported in equinus as evidence of initial contact planning[200]. Additionally, mild and moderate crouch had increased activation of W_1 through stance (C_1), due to a larger relative contribution of the quadriceps, and increased coactivation of the tibialis anterior and hamstrings through swing (C_2). In equinus-crouch walking, both W_1 and W_3 had increased activation in early stance following trends in crouch and equinus patterns, respectively. These differences corresponded to a significant difference between $tVAF_3$ and $tVAF_{3\_recon}$ (*i.e.,* tVAF by baseline weights) for all emulated patterns. Baseline weights accounted for 6.5% [5.2,11.7], 10.2% [7.1,14.5], 12.3% [10.4,18.4], and 19.1% [12.0,22.7] less of the variance in the EMG data for Eq,

Eq-Cr, Mi-Cr, and Mod-Cr gait, respectively, than the pattern-specific weights ($p < 0.001$ for all patterns).

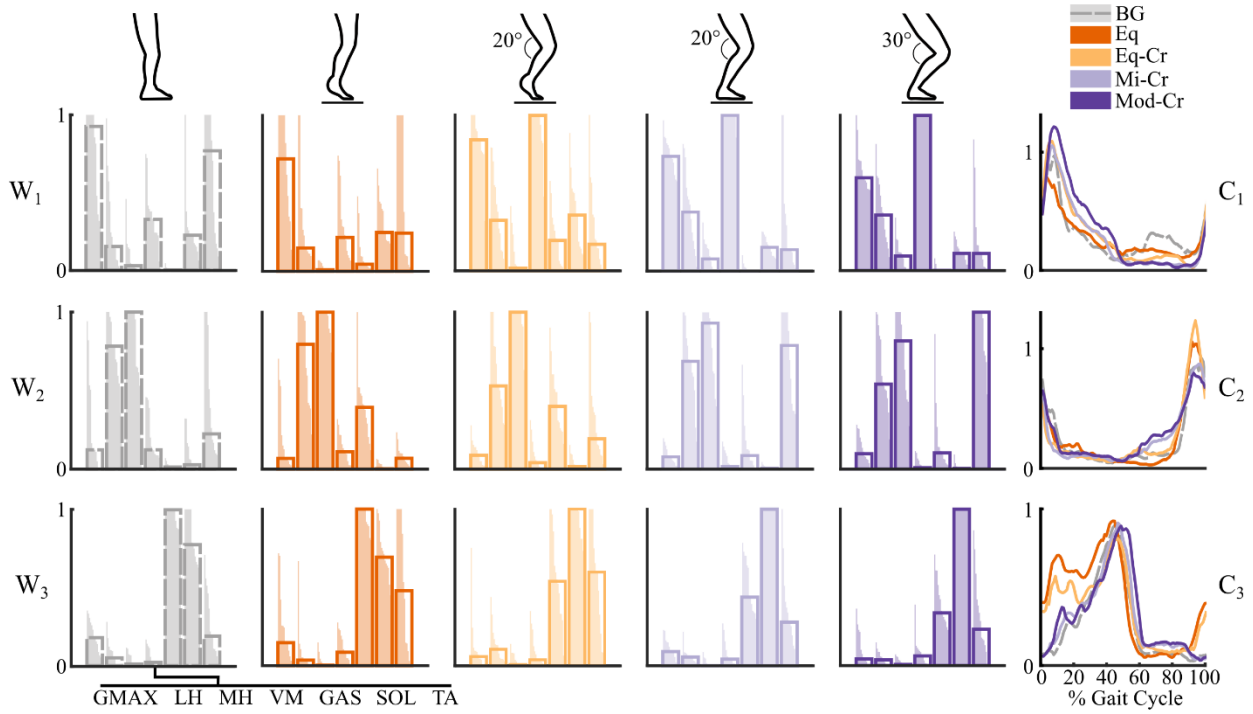

Figure 3.3 Synergy weights (W) and activations (C) for the three-synergy solution for baseline and emulated gait patterns. Median synergy weights across participants as well as synergy weights for each participant, sorted in descending value order, are displayed. Muscles: gluteus maximus (GMAX), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), medial gastrocnemius (GAS), soleus (SOL), and tibialis anterior (TA). Gait patterns: baseline, equinus (Eq), equinus-crouch (Eq-Cr), mild crouch (Mi-Cr), and moderate crouch (Mod-Cr).

3.3.3 Comparison to CP

Comparing emulated gait synergies to the CP cohort, notable differences in both structure and complexity emerged (Figure 3.4). Despite both cohorts having similar kinematics, $tVAF_1$ was significantly larger in the CP cohort than the TD cohort for all gait patterns except equinus (Table 3.2). This indicates that the CP cohort generally relied on less complex motor control during gait than ND individuals emulating similar patterns. This difference in control is further supported when looking at synergy structure. When *k*-means clustering was performed on the two-synergy

solution, four unique synergies emerged for the ND cohort compared to two synergies for the CP cohort (Figure 3.4). Synergies dominated by the tibialis anterior (W_1) and the hamstrings (W_2), emerged in both cohorts. However, in W_2, the CP cohort also had increased quadricep and gastrocnemius activity that was not consistently observed in the ND cohort. The ND cohort also had unique synergies dominated by (1) the tibialis anterior and gastrocnemius (W_{ND1}), which emerged for the majority of individuals during equinus gait and (2) the quadriceps (W_{ND2}), which emerged for the majority of individuals during equinus-crouch, mild crouch, and moderate crouch.

Table 3.2 Motor control complexity ($tVAF_1$) during ND emulated gait patterns compared a CP cohort.

	$tVAF_1$ (%)		
Gait Pattern	**CP Cohort (N = 28/pattern)**	**ND Cohort (N = 14)**	**p**
Equinus	77.0 [73.2,81.3]	79.1 [76.3,82.4]	0.4
Equinus Crouch	79.5 [76.2,83.4]	73.4 [68.8,76.0]	0.001*
Mild Crouch	78.0 [73.0,82.0]	70.8 [67.4,72.1]	<0.001*
Moderate Crouch	80.0 [76.4,84.3]	73.7 [69.3,76.7]	0.002*

Note: Values are listed as median [IQR]
*Significant difference ($\alpha < 0.05$) between CP and ND cohorts using Mann-Whitney U tests

3.4 Discussion

Although ND individuals were able to emulate CP gait, synergies did not deviate largely from baseline measures and, importantly, were distinct from synergies recruited by individuals with CP walking in similar patterns. However, emulation did alter synergy activations and inconsistently affected synergy complexity *(i.e.,* tVAF). These results collectively suggest that synergies in CP are not solely a reflection of altered gait patterns but rather capture aberrant neurophysiology.

3.4.1 Synergies are invariant to imposed biomechanical constraints

Three synergies emerged across all gait patterns, indicating that synergy weights were largely invariant to imposed biomechanical constraints. It is important to note that while > 74% of the

variance was captured when using baseline weights to reconstruct muscle activity during emulated gait patterns, there was a significant difference between $tVAF_3$ and $tVAF_{3\_recon}$ for all gait patterns. However, this difference was largely due to changes in the relative magnitude of muscle activations; importantly, similar muscles were recruited in each synergy across gait patterns.

The observed similarity of synergy weights during baseline and emulated gait patterns aligns with previous work. In ND adults, prior work has found that similar synergies are recruited with varying gait speed[46], incline[107], bodyweight loading[109], and stepping condition[108]. This observation also extends to clinical populations where synergy structure was similar following surgical intervention and gait biofeedback training in CP[34,35] and across stepping patterns in stroke[108], despite significant changes in gait. Further, children with Duchenne Muscular Dystrophy who had altered gait due to non-neurological muscle weakness (*i.e.* another form of biomechanical constraint) were shown to have similar synergy structure as ND children[215,216]. However, our study and prior work also suggest a relationship between changing biomechanical constraints and synergy activations. Shuman et al. (2019) observed that although synergy weights were unchanged following surgical interventions in CP, individuals whose synergy activations became more similar to ND trends after surgery had greater improvements in gait. Similar outcomes were reported by Rouston et al. (2013) who found that stroke survivors who improved synergy activation timing following training had greater improvements in walking performance. These findings suggest that for both ND and clinical populations, adaptability to imposed biomechanical constraints is maintained by tuning the activation of a consistent set of synergies.

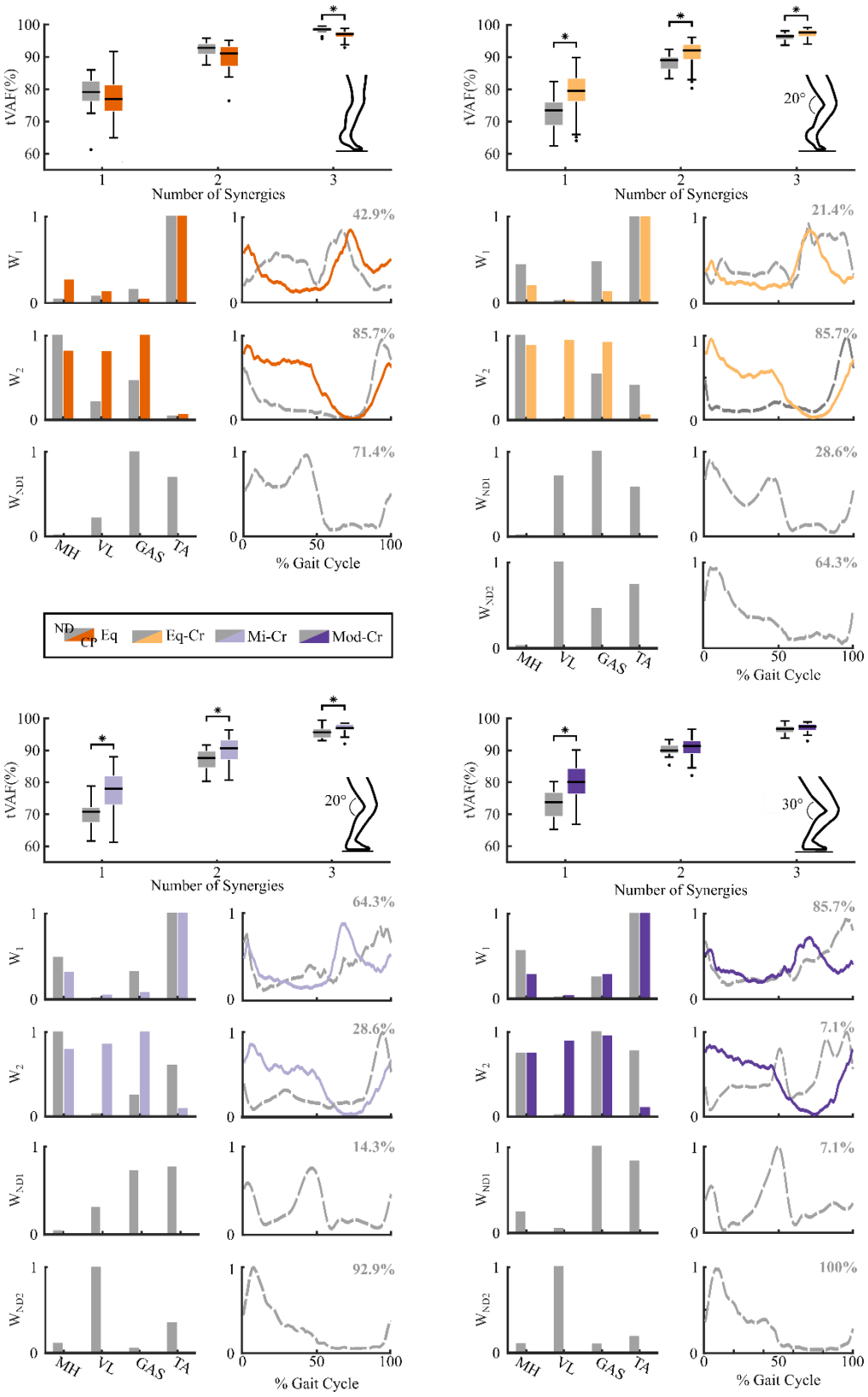

Figure 3.4 Synergy weights (W), activations (C), and complexity (tVAF) for the ND and CP cohorts during equinus (Eq), equinus-crouch (Eq-Cr), mild crouch (Mi-Cr), and moderate crouch (Mod-

*Cr) gait. Synergy weights for both CP and ND groups represent the two-synergy solution. K-means clustering was performed on each group and resulted in two clusters for the CP cohort (W1 and W2) and four clusters for the ND cohort (W1, W2, WND1 and WND2). Percentages reflect the number of ND individuals that recruited each synergy. * denotes significant difference between ND and CP for each n using Mann-Whitney U tests ($\alpha = 0.05$) and dots indicate outliers. Muscles: medial hamstring (MH), vastus lateralis (VL), medial gastrocnemius (GAS), and tibialis anterior (TA). Note that in the ND cohort, the vastus medialis was used in place of the VL, as the VL was not collected experimentally.*

3.4.2 Synergy complexity may be sensitive to gait pattern

Our results also highlight that changes in synergy activations can impact measures of synergy complexity. We observed that equinus-crouch, mild, and moderate crouch patterns did not affect complexity; however, equinus increased tVAF. This suggests that tVAF may be elevated for individuals who walk in an equinus pattern due to biomechanical constraints. Similar observations have been made regarding spasticity, as selective dorsal rhizotomy has been shown to increase $tVAF_1$ due to the pre-operative spasticity masquerading as more complex control[35]. These results have important clinical implications as $tVAF_1$ has been used to predict treatment outcomes in CP. Prior research has suggested that children with CP who have lower $tVAF_1$ have greater improvements in gait after common interventions[121]. As such, the sensitivity of synergy complexity to biomechanical constraints needs to be considered when using this measure in clinical decision making.

3.4.3 Emulated gait synergies do not align with synergies in CP

For all gait patterns, synergies were different between ND and CP cohorts, despite the groups being kinematically-matched. The CP cohort had increased coactivation of the hamstrings and quadriceps in all gait patterns, resulting in two synergies that generally aligned with swing and stance phase, similar to rhythmic-stepping patterns in infants[36]. In contrast, four unique synergies emerged in the ND cohort. The additional synergies identified in the ND cohort may suggests that the ND nervous system is more flexible to changing biomechanical constraints and highlight a

shift in reliance from supraspinal mechanisms to spinal circuitry to control gait following neurologic injury[37]. This is supported by Rouston et al. (2014) who reported that post-stroke patients with more severe impairment (*i.e.*, less complex control) were unable to selectively tune synergy activation to accommodate task demand.

3.4.4 Methodological considerations

When evaluating the results of this study, certain limitations need to be considered. Gait patterns were performed in a non-randomized order (*i.e.*, Eq, Eq-Cr, Mi-Cr, Mod-Cr) introducing fatigue as a potential confounder. To mitigate fatigue, we required one-minute seated breaks between trials and closely monitored fatigue levels. Further, as prior work has reported that synergies are minimally affected during cyclic tasks performed to failure, we do not expect fatigue to significantly influence our reported outcomes[218]. Participants also had minimal experience walking in the emulated patterns, which may have introduced learning effects. While we attempted to attenuate these effects by only analyzing the final trial for each pattern, we recognize that motor control strategies may change as a function of experience on a time scale longer than we could capture[124]. However, prior work has demonstrated that repeated exposure to novel tasks decreases co-contraction and tVAF[124]. As such, if ND participants were given a longer acclimation time for each pattern, we would expect tVAF values to decrease, and, therefore, diverge further from CP values.

To compare ND emulation results to CP, we had to rely on retrospective data. These data were collected as part of routine care and therefore only included overground trials with a limited muscle set and number of strides. Because smaller data sets generally overestimate tVAF, we recalculated ND synergies using the same number of strides and muscles as the CP cohort[193,210]. While we were not able to control for differences in walking condition, we would expect the ND

cohort to walk with greater variability overground [219] which would decrease reported tVAF values and increase the difference between cohorts. During matching, we did not exclude individuals based on injury severity or intervention history. This was a consequence of our hypothesis; if a direct tie existed between gait and synergies, kinematically-matched cohorts should recruit the same synergies regardless of other inter-cohort differences. Similarly, because of the typical age of intervention in CP, there was a significant difference in age between ND and CP cohorts ($p < 0.001$). However, prior work by Dominici et al. (2011) demonstrated that synergies stabilize early in ND development and are not expected to change significantly between the ages tested. Finally, we did not match frontal plane kinematics between cohorts. While hip adduction kinematics generally aligned, others, particularly at the pelvis, deviated between cohorts. This highlights an inherent limitation of emulation studies in CP; many gait patterns are multiplanar making them difficult to comprehensively emulate. However, because the muscle set analyzed primarily drives sagittal plane motion, we do not expect that matching frontal plane kinematics would significantly impact our conclusions.

3.5 Conclusion

This study suggests that altered synergies are not primarily a reflection of gait patterns in CP, but likely capture underlying neurologic pathology. While these results lend credence to the clinical use of synergy analysis, they also suggest that targeting gait improvements during intervention may not produce meaningful changes in synergies. Whether synergies can be changed in CP remains largely unknown. There is evidence that synergies can be modified with long-term training[124] or exoskeleton assistance[220] in ND adults. Further, recent research has suggested that resistance training with an ankle exoskeleton in CP may improve synergy complexity[221]. However, more work is needed to understand the plasticity of synergies in CP. Identifying factors that

influence synergies will further inform the use of synergy analysis in clinical care and guide the development of interventions that can more consistently improve function for individuals with CP.

Chapter 4

MOTOR CONTROL COMPLEXITY CAN BE DYNAMICALLY SIMPLIFIED DURING GAIT PATTERN EXPLORATION USING MOTOR CONTROL-BASED BIOFEEDBACK

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4.1 ABSTRACT

Understanding how the central nervous system coordinates diverse motor outputs has been a topic of extensive investigation. While it is generally accepted that a small set of synergies underlies many common activities, such as walking, whether synergies are equally robust across a broader array of gait patterns or can be flexibly modified remains unclear. Here, we evaluated the extent to which synergies changed as nondisabled adults (n = 14) explored gait patterns using custom biofeedback. Secondarily, we used Bayesian Additive Regression Trees to identify factors which were associated with synergy modulation. Participants explored 41.1 ± 8.0 gait patterns using biofeedback, during which synergy recruitment changed depending on the type and magnitude of gait pattern modification. Specifically, a consistent set of synergies was recruited to accommodate small deviations from baseline, but additional synergies emerged for larger gait changes. Synergy complexity was similarly modulated; complexity decreased for 82.6% of the attempted gait patterns, however, distal gait mechanics were strongly associated with these changes. In particular, greater ankle dorsiflexion moments and knee flexion through stance, as well as greater knee extension moments at initial contact corresponded to a reduction in synergy complexity. Taken together, these results suggest that the central nervous system preferentially adopts a low-dimensional, largely invariant control strategy, but can modify that strategy to produce diverse gait patterns. Beyond improving understanding of how synergies are recruited during gait, study outcomes may also help identify parameters that can be targeted with interventions to alter synergies and improve motor control following neurological injury.

4.2 INTRODUCTION

Humans are capable of producing a broad array of movements, allowing for robust locomotion in diverse and unpredictable environments. To achieve this range of motor outputs, it has been hypothesized that the central nervous system (CNS) recruits a small number of synergies (*i.e.*, modes, modules), defined as groups of coactivating muscles; this architecture is believed to simplify control beyond activating muscles independently[43,45,222]. Numerous studies have evaluated this hypothesis experimentally, employing matrix decomposition techniques, such as non-negative matrix factorization, to extract synergies and their corresponding activation patterns from electromyography (EMG) data[102,103]. These studies have revealed that tasks such as walking[46,47], running[106,195] and cycling[110] share a small set of muscle synergies, despite being biomechanically distinct. Further, across tasks, changes in speed[107], incline[46,107], cadence[108], and body-weight loading[46,109] are shown to shift the phase or duration of synergy activations rather than change the structure of the synergies themselves. These observations suggest that modest changes in sensory input or biomechanical demand are accommodated by altering the activation of invariant synergies and lend credence to their centralized role in coordination[113,114]. However, whether synergies are equally robust across a greater subset of achievable gait patterns or can be actively modified during gait is largely unknown[42,43].

Because synergies generally align with the sub-tasks of walking (*e.g.*, push-off, weight acceptance), gait patterns which impose additional mechanical requirements or present large changes in somatosensory feedback may alter synergy recruitment[113–116]. This is supported by prior work in animal models which demonstrated that frogs recruit task-specific synergies during swimming, jumping, and walking which correspond to the unique biomechanical demands of each movement[223]. Similarly, humans recruit specific synergies during perturbation recovery tasks to

maintain mediolateral stability and reduce center of mass movement[114,116,224,225]. Importantly, such synergies emerge in addition to those shared with other tasks, which is used to suggest that the CNS flexibly draws from a limited library rather than deploying unique control strategies for every task[114].

Taken together, prior results indicate that a relationship exists between the biomechanical constraints of a given task and the recruited control strategy. That is, the CNS may preferentially tune the activation timing of a consistent set of synergies but is simultaneously capable of recruiting different synergies to produce diverse outputs. Understanding when and how synergies are modulated across changing biomechanical constraints and the factors driving this modulation is critical to better inform how the CNS coordinates complex movement. While this relationship has been previously characterized across broad balance[114,226] and finger force generation tasks[42,227], gait has not been studied to the same extent[108,228].

Beyond enhancing understanding of the neural control of gait, characterizing whether synergies can be modulated in walking may also inform methods for targeting aberrant synergy recruitment. Individuals with cerebral palsy[38,41,121], Parkinson's disease[120], and spinal cord injury[119] as well as stroke survivors[117,118] recruit fewer synergies than nondisabled peers which impacts independent mobility[117,229,230] and may reduce the efficacy of traditional interventions[121]. Because available interventions for these populations often fail to alter synergies[35], developing new paradigms to directly improve synergy recruitment has become a critical priority in gait rehabilitation. This has spurred the development of biofeedback and robotic gait training paradigms which have thus far yielded promising, yet still highly variable results[34,40,217]. As such, mapping the relationship between biomechanical constraints and synergy modulation may further

inform the design of these systems by highlighting gait parameters that can be directly targeted to produce greater and more consistent changes in motor control.

The aim of this study was to characterize the robustness of synergies to changing biomechanical constraints during walking. Specifically, we evaluated the extent to which nondisabled individuals could modulate both synergy structure and complexity while using motor control biofeedback to drive broad gait pattern exploration. These data were then used to build a Bayesian Additive Regression Trees (BART) model to identify biomechanical variables that were associated with synergy modulation. We hypothesized that changing biomechanical constraints would alter the recruitment but not the structure of muscle synergies, but that different synergies may be recruited to accommodate large deviations from baseline. The results from this investigation will provide further insight into the extent to which motor control can be altered and, importantly, improve understanding of how the CNS shapes its control strategy to produce a repertoire of motor outputs. The latter will support the development of intervention strategies to improve motor control among individuals with neurological injury.

4.3 METHODS

4.3.1 Experimental Protocol

A convenience sample of fourteen nondisabled individuals (7M/7F; Age: 24.1 ± 4.7 years; Height: 1.7 ± 0.1 m; Mass: 65.7 ± 20.1 kg) were recruited to evaluate synergies during gait pattern exploration. Prior to participation, all provided written informed consent and the experimental protocol was approved by the University of Washington Institutional Review Board.

Participants walked on an instrumented treadmill (1200 Hz; Bertec, Columbus, OH) at a self-selected speed (1.07 ± 0.13 m/s) while responding to a custom biofeedback system. Briefly, this system presented the participant with a score of their dominant-limb synergy complexity on a

graphical display, where a higher score corresponded to increased complexity (see Section 4.3.2; Figure 4.1).

Participants performed one baseline walking trial with the feedback system turned off followed by feedback trials during which they were instructed to either raise or lower their complexity score; two trials were performed in each target direction. All trials were three minutes long and separated by mandatory one-minute rest periods. During the feedback trials, participants were encouraged to explore a broad range of gait patterns to modify their score. The only imposed restrictions were that they must maintain forward-facing walking and take at least five consecutive strides in the pattern selected.

Surface EMG data (Delsys Inc, Natick, MA) were recorded bilaterally for seven lower limb muscles: gluteus maximus (GM), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), soleus (SO), tibialis anterior (TA), and medial gastrocnemius (MG). Raw EMG signals were low passed filtered (4^{th} order Butterworth; 20 Hz), rectified, and high pass filtered (4^{th} order Butterworth; 10 Hz) to establish linear envelopes[207]. After filtering, non-physiological signal spikes were removed using a robust-PCA algorithm[209] and the data were normalized to the 95^{th} percentile of maximum muscle activity across all trials.

Full-body motion data were collected using a 10-camera motion capture system (120 Hz) and a Helen Hayes marker set, modified to include the trunk and arms[231] For each participant, a generic 33 degree-of-freedom model (pelvis rotation (3) and translation (3), trunk (3), lower limbs (14), and upper limbs (10)) was linearly scaled in OpenSim v3.3 from maker data to match participant anthropometrics and mass[204]. Joint angles and moments were then derived from filtered maker and ground reaction force data (4^{th} order low-pass Butterworth filter; 6 Hz cutoff) using the inverse kinematics and dynamics tools[203]. The average root-mean-squared (RMS) and maximum

marker error for all subject models were 1.3 cm and 2.5 cm, respectively, which fall below the recommended thresholds for model fidelity[205].

4.3.2 Biofeedback System Design

The biofeedback system was custom designed in Python (Python Software Foundation) to calculate synergy complexity for the dominant leg and output to the user on a visual display (Figure 4.1). For each recorded stride, defined by heel strike, the system performed a one-synergy decomposition using EMG data for the just completed stride and four previous strides (*i.e.,* a sliding 5-stride window). $tVAF_1$ was then quantified and converted to a z-score (*i.e.,* complexity score), normalized to the participant's baseline walking condition. The z-score was scaled such that a score of 100 was equal to baseline complexity and larger number indicated greater synergy complexity; this scaling helped increase the overall interpretability of $tVAF_1$ for a broad user base. The visual display was updated with each stride and presented the user with their synergy complexity score alongside a green bar, which indicated the goal direction of change. We elected to use a sliding five-stride window, rather than calculate $tVAF_1$ for each stride independently, to improve the overall stability of the feedback metric. Due to the higher stride-to-stride variability expected during gait pattern exploration, we anticipated that $tVAF_1$ may vary significantly if the data for a single stride was used, which could negatively impact participant comprehension of the feedback system.

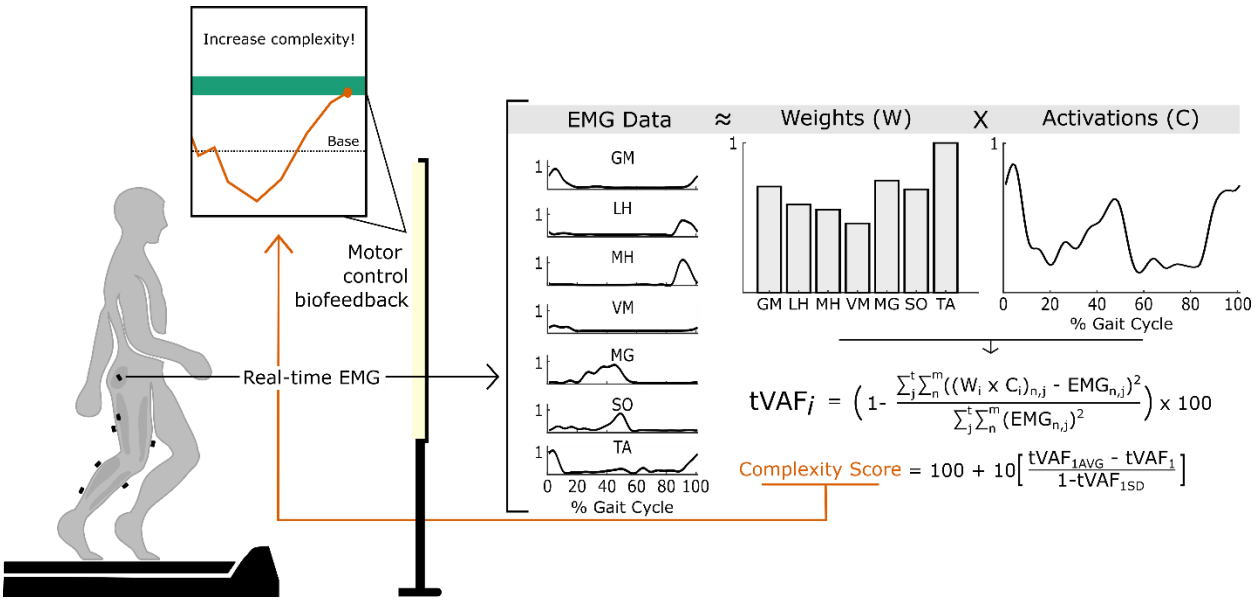

Figure 4.1 Schematic of the custom biofeedback system. For every new stride, non-negative matrix factorization is used to calculate the one-synergy solution, W_1, and the corresponding activation coefficient, C_1, from dominant-limb EMG data for a sliding 5-stride window. The total variance accounted for by the one-synergy solution ($tVAF_1$) represents the reconstruction accuracy of the synergy decomposition across all muscles, m, and time points, t. A z-score of $tVAF_1$ (complexity score) is then quantified and output to the user on a visual display, alongside a green bar, indicating the goal direction of change. The complexity score is scaled such that an increase corresponds to an increase in motor control complexity. The mean ($tVAF_{1AVG}$) and standard deviation ($tVAF_{1SD}$) in the complexity score calculation are quantified for each participant from baseline data. Muscles: gluteus maximus (GM), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), soleus (SO), tibialis anterior (TA), and medial gastrocnemius (MG).

4.3.3 Gait Analysis

Because participants explored many different gait patterns using the biofeedback system, we first had to extract each pattern attempted across trials and participants (Figure 4.2). To do this, the gait deviation index (GDI) was calculated from the kinematic data for every stride in each trial[232]. The GDI is a summary measure of deviations in pelvis (tilt, list, rotation), hip (adduction, rotation, flexion), knee (flexion), and ankle (flexion) kinematics from 'normative' trends and was, therefore, expected to change during gait pattern exploration. For each trial, groups of five or more consecutive strides with similar GDI values were automatically labeled as individual gait patterns; each gait pattern identified was then subsequently confirmed via manual inspection to ensure

appropriate labeling. Following labeling, average kinematic and kinetic trends at the pelvis, hip, knee, and ankle were quantified for each gait pattern. To identify kinematically-similar strategies adopted by multiple participants, the pelvis, hip, knee, and ankle kinematics for all patterns were separated into clusters (K_1 to K_N) using the k-means clustering approach outlined in Rozumalski and Schwartz (2009).

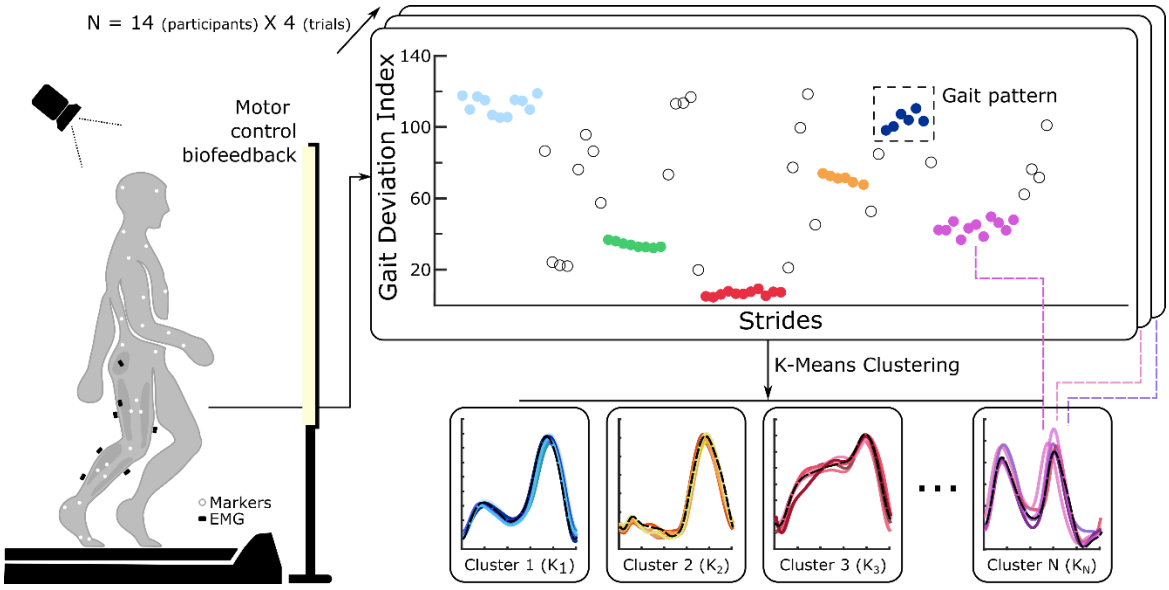

Figure 4.2 Methodology used to identify clusters (K_1 to K_N), representing kinematically-similar gait patterns attempted by participants during feedback walking. Full-body kinematic and kinetic data and lower-limb EMG data were collected while participants explored a broad range of gait patterns using biofeedback. The Gait Deviation Index (GDI) was calculated from kinematic data for each recorded stride for every participant and trial (56 data sets). Individual gait patterns were labeled as five or more consecutive strides with similar GDI values and manually confirmed. Kinematic data for these patterns were input into a k-means clustering algorithm to identify clusters (K_1 to K_N) across participants and trials.

4.3.4 Synergy Analysis

Muscle synergies were quantified from EMG data for each gait pattern using non-negative matrix factorization (NMF). NMF is a linear matrix decomposition technique which is commonly used to identify non-negative synergies (W) and their corresponding activations (C) from EMG data, such that $EMG_{mxt} = W_{mxi} * C_{ixt} + error$ where m is the number of muscles, i is the number of synergies,

and t is the time points[101,103]. The structure of the W and C matrices provide insight into how muscles coactivate across the gait cycle. Similarly, the total variance accounted for (tVAF) by a given number of synergies (i) is used as a summary measure of control complexity; a comparatively higher tVAF value for the ith synergy solution indicates that the variance in the EMG data can be well-captured by a low-dimensional subspace and, therefore, that the muscle activation patterns are less complex. Importantly, tVAF is associated with impairment level, as individuals with neurological injury[38,41,117–121] have higher tVAF values (*i.e.* less complex control) for a given synergy solution than nondisabled peers. Therefore, if synergies were sensitive to imposed biomechanical constraints, we may expect to see changes in both synergy structure and complexity measures.

We calculated $i = 1$ to 7 synergies using the dominant-limb EMG data for five concatenated strides for each gait pattern attempted. Because synergy analysis is sensitive to the amount of EMG data used, we elected to analyze a consistent number of strides across all patterns and participants[210]. If a participant took more than five strides in a pattern, we performed a bootstrapping procedure by quantifying synergies using five random strides, selected with replacement from the available set, and replicating this process until a normal distribution was achieved; average synergies and tVAF values were then reported. The same bootstrapping procedure was performed on the baseline walking data with sets of five concatenated strides (replicates = 200) to ensure accurate comparisons between baseline and feedback conditions.

We evaluated synergy structure during gait pattern exploration in two ways. We first compared the inter-cluster (K_1 to K_N) similarity of synergy weights (W) and activation patterns (C) for the $i = 3$ synergy solution. This solution was evaluated, as three synergies explained over 90% of the variance in EMG data for the majority of gait patterns. We sorted synergy weights for

all gait patterns attempted during exploration as well as baseline walking into *k* clusters[211]. Because individuals may recruit different synergies during exploration compared to baseline gait, we varied *k* between *k = 3* (*i.e.*, synergies were consistent between baseline and exploration) and *k* = 10**3* (*i.e.,* different synergies emerged during exploration) and selected *k* as the number of clusters with the maximum silhouette coefficient [212]; the upper bound on *k* was highly conservative and based on our expectation that synergies would be predominantly shared across gait patterns[114]. Synergy weights and activations for each gait pattern were then sorted into their respective clusters (K_1 to K_N) and the average values were calculated. Secondarily, we evaluated the intrasubject similarity of baseline synergies with those recruited during exploration. This was done by fixing the W matrix as the synergy weights extracted from baseline walking for the three-synergy solution (*i = 3*) and using the multiplicative update rule from NMF to find a C matrix which minimized the error between W*C and the EMG data for each gait pattern that an individual attempted. From this, we were able to calculate the total variance that could be explained in each gait pattern by baseline weights ($tVAF_{3\_BASE}$) which was then compared to the $tVAF_3$ values (*i.e.*, those calculated directly from the EMG data for each gait pattern), yielding a measure of synergy similarity. If similar synergies were recruited during gait pattern exploration and baseline walking, we would expect $tVAF_{3\_BASE}$ and $tVAF_3$ to be similar.

Table 4.3 BART Model Variables

Response	Description
$\Delta tVAF_1$	Difference in motor control complexity between each unique gait pattern and baseline walking.

Predictors	Description
Baseline $tVAF_1$	Measure of motor control complexity during the baseline walking condition. Values range from 0 - 1, where a higher value indicates less complex control.
Participant Number	Values range from 1-14. This variable was used to evaluate if participant-level differences in biofeedback exploration emerged.
Speed	Nondimensional walking speed normalized to participant leg length.
Kinematics/Kinetics	Mean values of all variables outlined in Figure 4.3. Variables input as z-scores, normalized to baseline walking. These variables were selected as they sufficiently capture kinematic/kinetic trends during the gait cycle.
Kinematic/Kinetic Variability	Difference in the standard deviation of all variables outlined in Figure 3 between each unique gait pattern and baseline walking. These variables reflect the participant's ability to consistently produce the attempted gait patterns.

4.3.5 Statistical Analysis

4.3.5.1 Cluster-wise comparisons

For each cluster (K_1 to K_N), we compared mean tVAF values to (1) baseline walking and (2) $tVAF_{BASE}$ using paired t-tests to evaluate if synergy complexity or structure changed during gait pattern exploration, respectively. Secondarily, one-way ANOVA tests were used to compare if synergy complexity and structure were similar between clusters (K_1 to K_N); for any test that reached significance, t-tests were used to perform pairwise comparisons. Average joint angles in swing and stance phases for each cluster (K_1 to K_N) were also compared to baseline walking using paired t-tests. To characterize stride-to-stride variability, the standard deviation of the average stance and swing phase joint angles during exploration were also compared to baseline using paired t-tests. For all comparisons to baseline walking and post-hoc analyses, p-values were adjusted using a Holm-Šídák correction to account for multiple tests. We defined significance as $p < \alpha$ for $\alpha = 0.05$ and report mean values ± 1 SD unless otherwise indicated. All cluster-wise

statistical analysis was performed using the MATLAB Statistical Toolbox (MathWorks, Natick, USA).

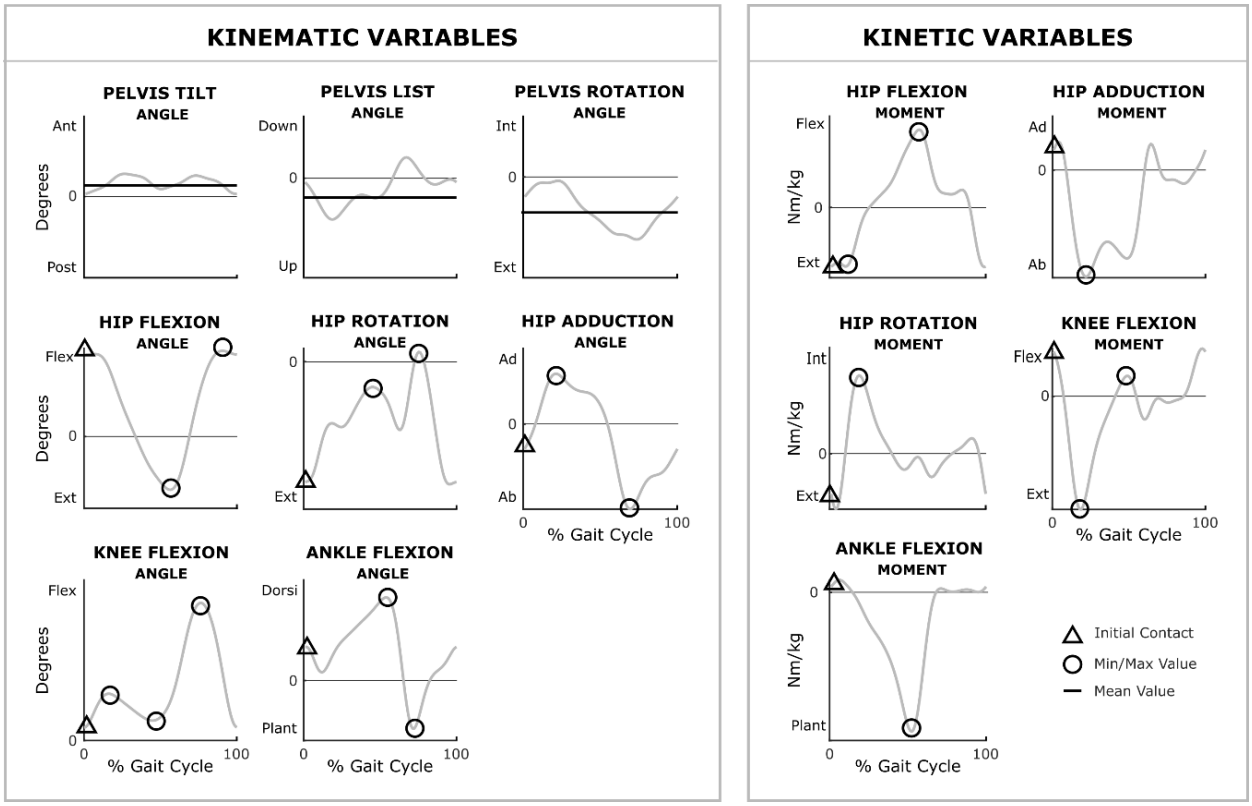

Figure 4.3 Kinematic and kinetic input variables included in the BART model. Each icon indicates a variable (n = 31 total) that was identified for every gait pattern. Variables were selected to capture trends at the pelvis, hip, knee, and ankle that could change during exploration. Circles indicate local maximum or minimum values, and triangles indicate initial contact points, calculated as the mean value over the first 5% of the gait cycle. Average pelvis list, tilt, and rotation angles across the gait cycle were included to capture asymmetries. The standard deviations of each kinematic and kinetic variable, used to capture stride-to-stride variability during gait pattern exploration, were also included in the input variable set.

4.3.5.2 BART analysis

To further examine the relationship between gait pattern exploration and synergy complexity, we developed a Bayesian Additive Regression Trees (BART) statistical model[233]. BART is a 'sum-of-trees' machine learning algorithm , similar to other common techniques such as boosting[234,235] and random forests[236]. However, unlike other methods, BART uses a Bayesian probability model

to control the depth of individual trees in order to prevent data overfitting[233,237]. BART was selected for this application due to its favorable predictive performance compared to other machine learning techniques and because it can capture the non-linear relationships inherent in motion data[233,238,239].

We used BART to model changes in synergy complexity during exploration compared to baseline walking, quantified as the difference in total variance accounted for by a one-synergy solution (*i.e.*, $\Delta tVAF_1$). We selected $tVAF_1$ as our primary outcome given its clinical relevance; prior work has demonstrated that $tVAF_1$ is predictive of surgical outcomes[121–123] and associated with walking function [38,41,117–120] in populations with neurologic injury, making it critical to understand the factors which may be associated with $tVAF_1$ modulation. Our input set (Table 4.3) included kinematic and kinetic variables that characterized each gait pattern as well as other metrics which could influence the type of gait patterns a participant attempted. When defining kinematic and kinetic input variables, we prioritized a set that captured the changes observed at the pelvis, hip, knee, and ankle during exploration, while simultaneously maintaining input set conciseness. These criteria resulted in the variables outlined in Figure 4.3 (n = 31). For each of the identified kinematic and kinetic variables, both the mean and standard deviation values are included as inputs, normalized to baseline walking. We elected to include the latter, as $tVAF_1$ is sensitive to the amount of variance in the data and could, therefore, be affected by individuals simply moving with greater stride-to-stride variability, as might be expected during novel gait pattern exploration [124]. We tuned hyperparameters for the developed BART model using 10-fold cross-validation (parameters: k = 3, q = 0.9, nu = 3, num_trees = 200, seed = 30) Kapelner and Bleich 2016) and report both pseudo-R^2 and the out-of-sample root-mean-squared error (RMSE) as metrics of model quality.

Outputs from the BART model were interpreted with accumulated local effect (ALE) plots[240]. ALE plots are used to visualize the effect that individual input variables have on the specified response (*i.e.*, $\Delta tVAF_1$), conditioned on all other model covariates. Unlike partial dependence plots, which are also commonly used to this end, ALE plots are generated by averaging and accumulating the local rather than marginal effects of each input, making them unbiased in cases where input variables are highly correlated; this is particularly advantageous for this application, due to the high level of correlation between kinematic and kinetic variables during gait.

Because ALE plots are generated by sampling from the available data, some discrepancy between the 'true' and 'estimated' effect is expected[240]. To capture this uncertainty, we performed a boostrap analysis (n = 100 replicates), drawing samples with replacement from the original data set to generate a series of ALE plots from which the average and standard deviation could be quantified. Using these average plots, we approximated net effects for each input variable as the difference between the 95th and 5th percentile of the response. If synergies were sensitive to biomechanical constraints during gait pattern exploration, we would expect both kinematic and kinetic variables to have large net effects on $\Delta tVAF_1$. BART model development and ALE plot generation were performed in RStudio (RStudio Team, 2020) using the *bartMachineCV* and *ALEPlot* packages[237,240].

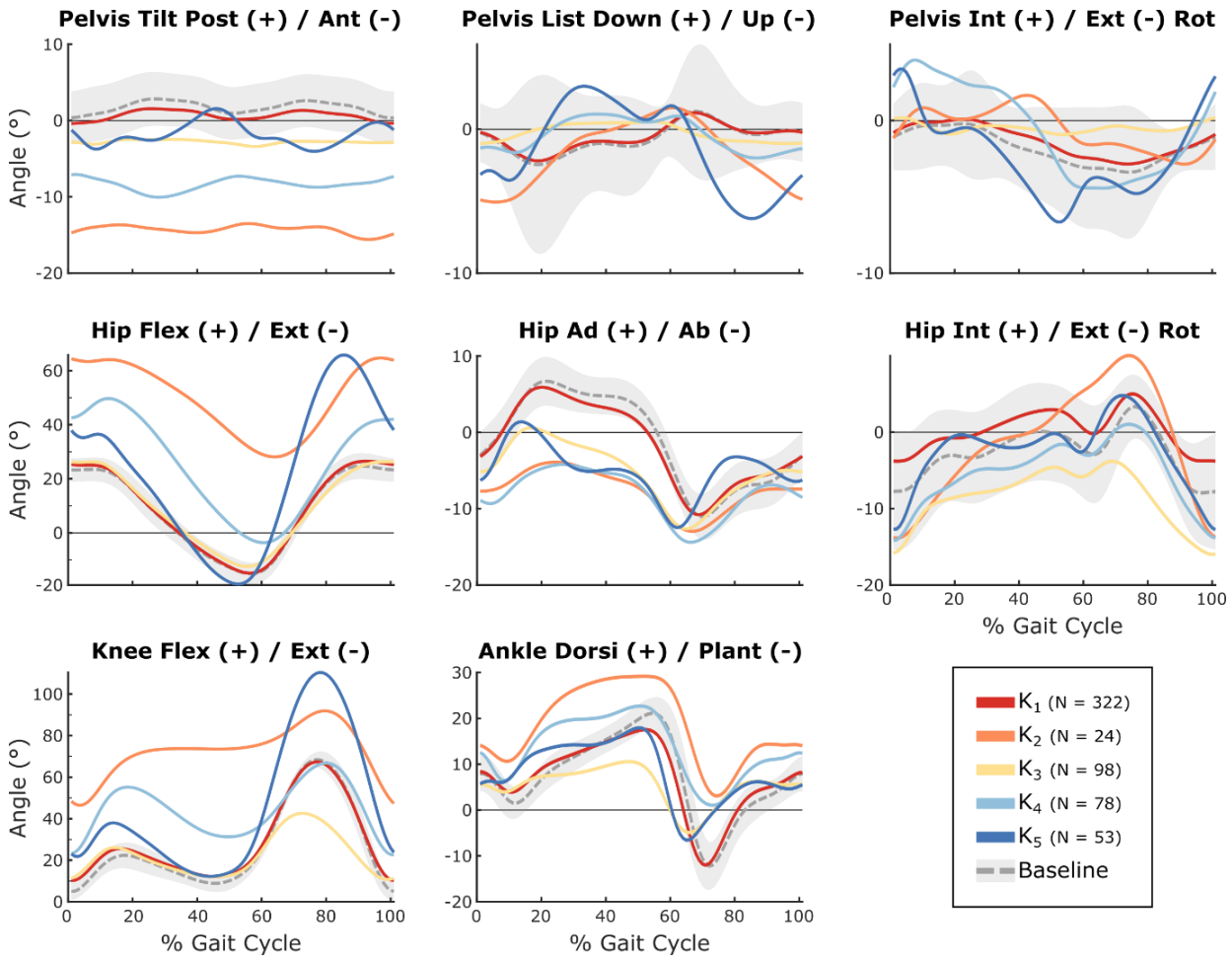

Figure 4.4 Average pelvis, hip, knee, and ankle kinematics for the five clusters identified by k-means clustering ($K_1 – K_5$), representing common gait patterns attempted during exploration. The baseline condition shows ± 1SD.

4.4 Results

4.4.1 Gait Exploration

Participants explored 10.3 ± 2.8 gait patterns per feedback trial on average, resulting in 575 total patterns across all participants. These data were separated into five clusters, representing the common kinematic strategies attempted (Figure 4.4). K_2 and K_4 represented 24 and 78 gait patterns, respectively, and were characterized by increased hip flexion (K_2: 47.7 ± 11.3°; K_4: 23.1 ± 8.8°), knee flexion (K_2: 70.6 ± 9.1°; K_4: 40.9 ± 11.1°), hip abduction (K_2: 7.4± 7.0°; K_4: 7.7 ± 7.6°), anterior pelvic tilt (K_2: 14.1 ± 6.6°; K_4: 8.4 ± 7.9°), and ankle dorsiflexion (K_2: 20.7 ± 2.7°;

K_4: 15.6 ± 5.2°) through stance compared to baseline. K_3 represented 98 gait patterns defined by greater anterior pelvic tilt (2.8 ± 3.7°), hip abduction (3.9 ± 4.2°), and plantarflexion (6.3 ± 8.9°) through stance, as well as decreased knee flexion through swing (29.8 ± 9.1°). K_5 included patterns with increased hip (44.7 ± 12.2°) and knee flexion (80.0 ± 10.1°) during swing and increased hip abduction (4.5 ± 3.5°) in stance. Finally, K_1 included 322 gait patterns that aligned closely with baseline trends ($p > 0.054$ for all angles), capturing points within the feedback trials in which participants were minimally exploring. Corresponding kinetic trends for each cluster can be found in Figure A.1.1.

As expected, stride-to-stride variability increased for all kinematic parameters in K_2 to K_5 ($p < 0.05$ for all parameters), with the largest variability seen in gait patterns in K_2. This increase in variability highlights an inherent learning effect associated with gait pattern reproduction. Even when participants were minimally exploring (*i.e.,* K_1), there was generally an increase in variability compared to baseline, likely due to the added attentional demand of responding to the biofeedback system.

4.4.2 Synergy Analysis

All participants were able to significantly modify synergy complexity during exploration (Figure 4.5). A one-synergy decomposition ($i = 1$) accounted for 66.1 ± 5.9% of the variance in the EMG data during baseline. When clustered, $tVAF_1$ was 71.6 ± 7.2% (K_1), 78.3 ± 6.6% (K_2), 76.5 ± 6.4% (K_3), 76.0 ± 6.2% (K_4), and 69.8 ± 5.7% (K_5), indicating that all of the explored patterns significantly decreased complexity from baseline ($p < 0.05$). Interestingly, there were also significant inter-cluster differences in $tVAF_1$, suggesting that the type of gait pattern modification impacted complexity ($p < 0.001$). It should be noted that although participants were instructed to either raise or lower their synergy complexity scores, minimal differences existed between these

trials, participants generally decreased complexity regardless of the target direction. As such, we did not conduct further analyses comparing target directions.

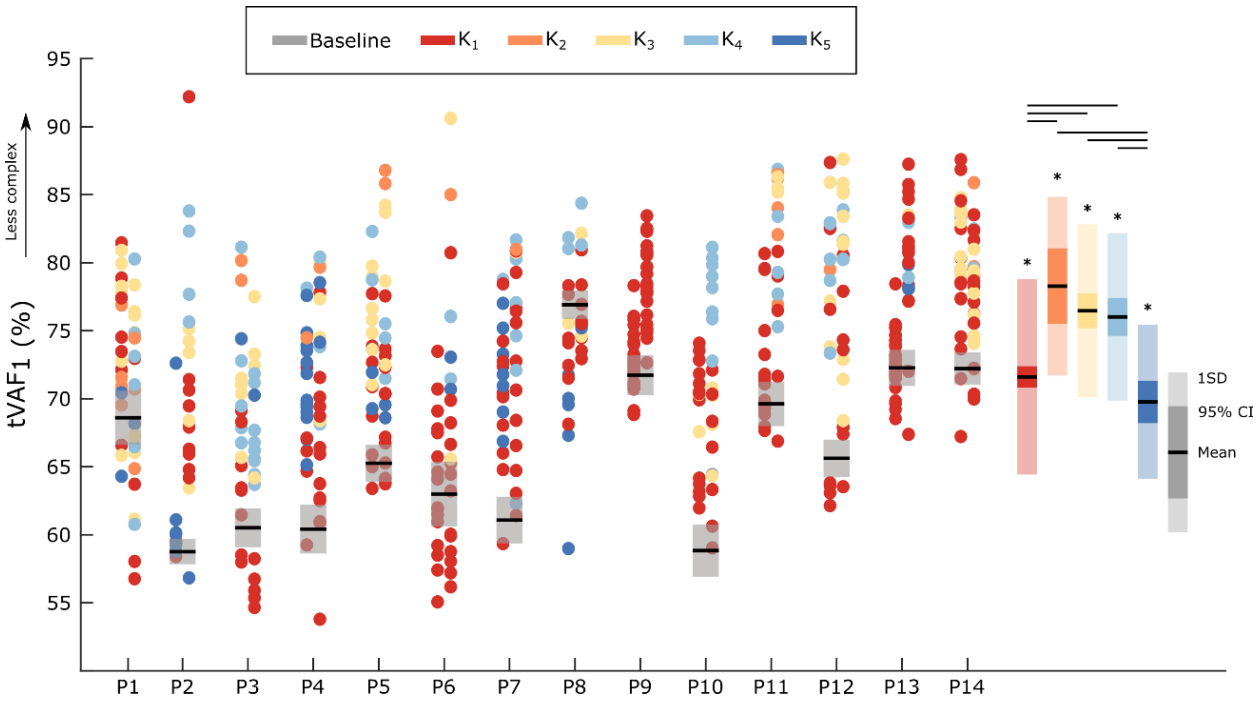

*Figure 4.5 The total variance accounted for by a one-synergy solution ($tVAF_1$) for each participant (P1-P14). Each dot represents an individual gait pattern and is colored according to the cluster it was sorted into (K_1 to K_5). For each participant, data is organized into two columns representing the feedback trials in which participants were instructed to decrease (left) and increase (right) their synergy complexity ($tVAF_1$). Baseline data is presented as a mean ± 1SD, representing the distribution of $tVAF_1$ values resulting from bootstrapping using sets of five random strides (replicates = 200). Summary box plots, located to the right of the participant data, represent the mean (black line), 95% confidence interval (solid color), and standard deviation (shading) of $tVAF_1$ values for each cluster and baseline walking. Larger $tVAF_1$ values correspond to decreased motor control complexity. * denotes significant difference between each group and the baseline condition and black bars indicate significant inter-cluster differences ($\alpha = 0.05$).*

A three-synergy solution (i = 3) accounted for 92.6 ± 2.3% of the variance for all exploration and baseline walking patterns. Clustering yielded four distinct synergy structures (Figure 4.6) that were dominated by the TA (W_1), hamstrings (W_2), the quadriceps and gluteus maximus (W_3), and the plantarflexors (W_4). All four synergy structures were observed across K_1 to K_5 as well as baseline walking but were recruited with varying frequency. For example, baseline

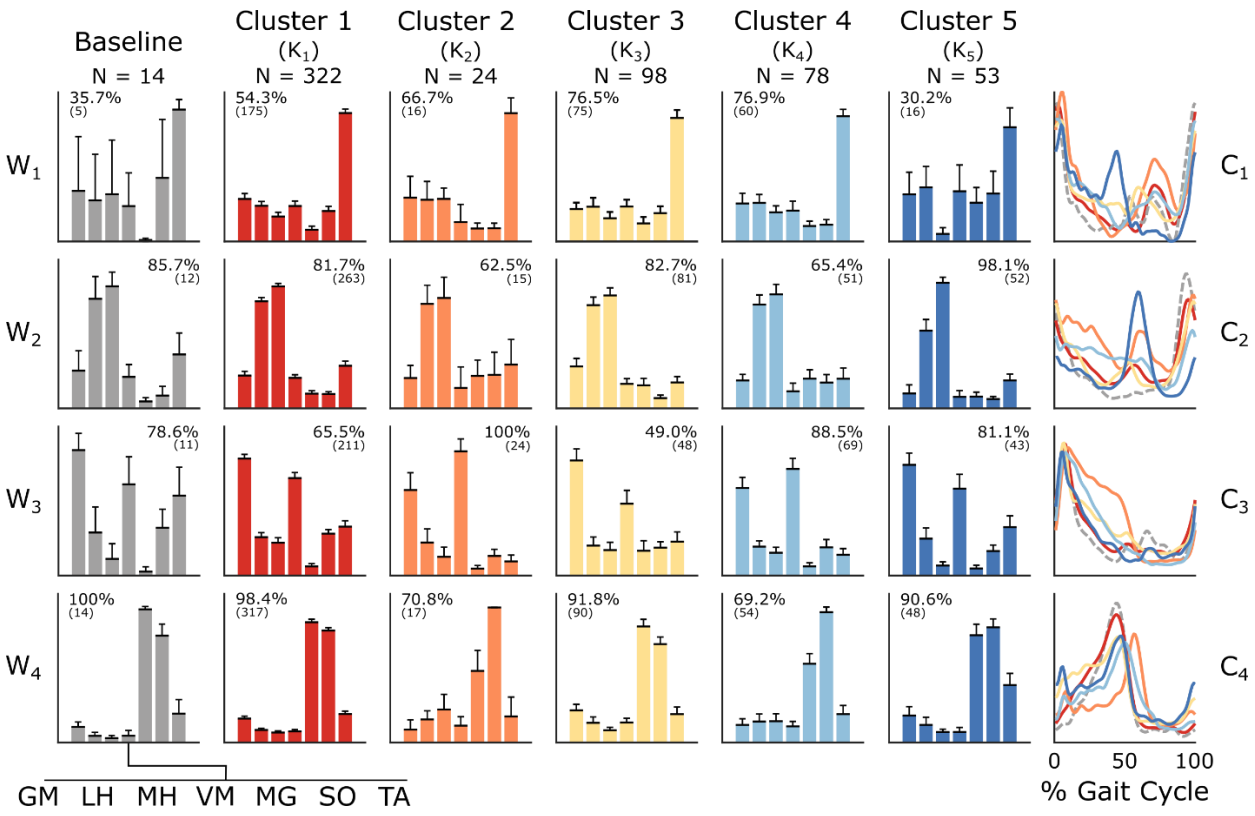

Figure 4.6 Average synergy weights (W) and activations (C) for the three-synergy solution for baseline walking and each cluster of kinematically-similar gait patterns (K_1 to K_5). K-means clustering was performed for the i = 3 synergy solution across all gait patterns and yielded four unique structures. Synergy weight plots reflect cluster-wise averages and error bars show the 95% confidence interval. The numbers in the corner of each plot reflect the percentage (total number) of gait patterns within each cluster (i.e., K_1 to K_5) that used each synergy. Muscles: gluteus maximus (GM), lateral hamstrings (LH), medial hamstrings (MH), vastus medialis (VM), medial gastrocnemius (MG), soleus (SO), and tibialis anterior (TA).

walking was primarily defined by W_2, W_3, and W_4, which were present in 85.7%, 78.6%, and 100% of gait patterns in the group, respectively. These synergies align with those previously reported in nondisabled adults during steady-state walking[47,117]. In contrast, K_3 was dominated by W_1 (76.5%), W_2 (82.7%), and W_4 (91.8%). Interestingly, the plantarflexor synergy (W_4) emerged for the majority of patterns in all clusters (K_1 to K_5) whereas W_1, W_2, and W_3 were differentially recruited. These results suggest that a small pool of synergies exists that can be selectively drawn from depending on the biomechanical constraints of a given pattern. Across groups, synergy activation patterns were also distinct from baseline and aligned with key kinematic trends. For

example, K_2 was characterized by increased knee flexion and ankle dorsiflexion through the gait cycle, which was reflected in the increased activation of W_1 in swing and W_3 through stance.

The observed change in synergies recruited during exploration corresponded to an overall decrease in $tVAF_{3\_BASE}$ when baseline synergy weights were used to reconstruct EMG data from exploration trials (Figure 4.7; $p < 0.001$ for all groups). For the three-synergy solution, baseline synergy weights accounted for $6.0 \pm 6.0\%$ (K_1), $17.7 \pm 11.0\%$ (K_2), $10.6 \pm 8.0\%$ (K_3), $15.3 \pm 8.7\%$ (K_4), and $11.3 \pm 7.1\%$ (K_5) less of the variance in EMG data than weights extracted directly from each pattern. Further, the similarity of synergy structures to baseline was different between clusters ($p < 0.001$), with the largest difference seen in K_2. This suggests that baseline synergy weights captured more of the variance in muscle activity for certain gait patterns than others, further confirming the flexible recruitment of synergies to changing biomechanical constraints.

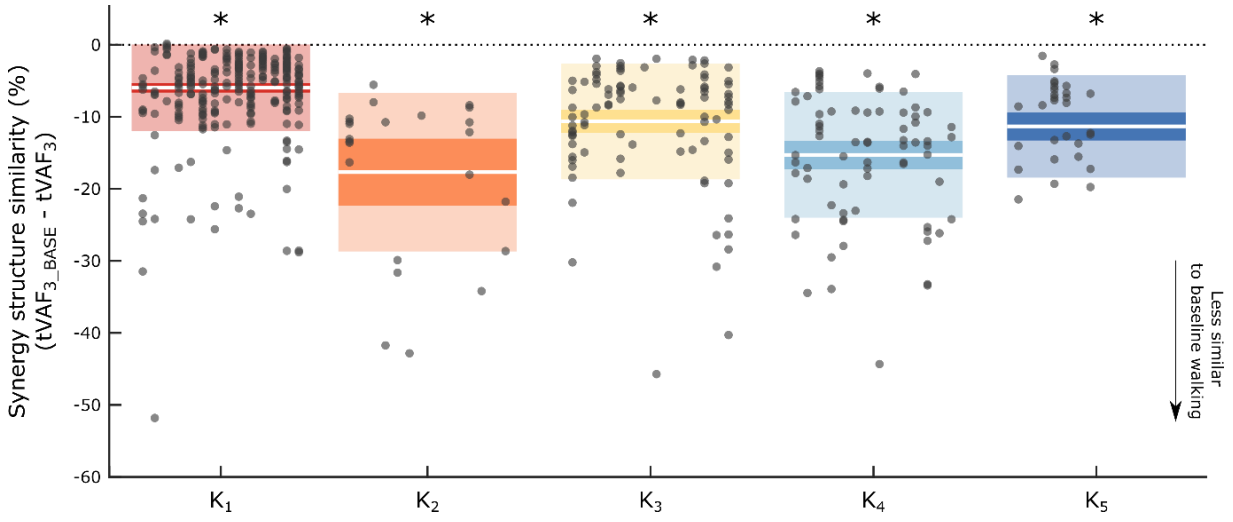

Figure 4.7 Similarity of the i = 3 synergy solution for each cluster (K_1 to K_5) as compared to baseline walking. $tVAF_{3\_BASE}$ represents the amount of variance accounted for when baseline synergy weights are used to reconstruct EMG data for all gait patterns within each cluster whereas $tVAF_3$ represents the variance accounted for by weights extracted directly from EMG data for each gait pattern. A larger difference between $tVAF_{3\_BASE}$ and $tVAF_3$ indicates that baseline synergies captured less of the variance in the EMG activity measured during gait pattern exploration and, therefore, that synergies recruited were less similar to baseline. For each box, white bars represent mean values, the solid-colored blocks represent a 95% confidence interval,

*and shading shows ±1 SD. Dots represent individual gait patterns and are arranged in columns to represent individual participants (P1 to P14). * indicates a significant difference in synergies from baseline walking.*

4.4.3 BART Analysis

The BART model was able to explain changes in synergy complexity observed during exploration (R^2 = 0.88; RMS error = 4.4). Baseline $tVAF_1$ had the largest net effect (4.6%) on $\Delta tVAF_1$, as individuals with higher baseline complexity increased $tVAF_1$ to a greater extent during exploration than those with lower baseline complexity (Figure 4.9). However, this observation partially reflects the effects of regression to the mean. After baseline $tVAF_1$, kinematic and kinetic input variables, especially those at the knee and ankle, had the largest effects on $\Delta tVAF_1$ (Figure 4.10A). In particular, greater knee flexion (net effect = 3.2%), anterior pelvic tilt (2.3%), hip extension moment (2.7%), and ankle dorsiflexion moment (2.8%) through stance corresponded to a greater decrease in synergy complexity. Increased knee extension moment (net effect = 3.1%) at initial contact also corresponded to less complex control. Interestingly, only one swing-phase variable had a large effect on $\Delta tVAF_1$; decreased knee flexion during swing resulted in greater decreases in synergy complexity (net effect = 3.3%). Further, two measures of kinematic and kinetic variability emerged among the top inputs in the BART model (Figure 4.10B), highlighting the sensitivity of synergy complexity to the increased stride-to-stride variability observed during gait pattern exploration.

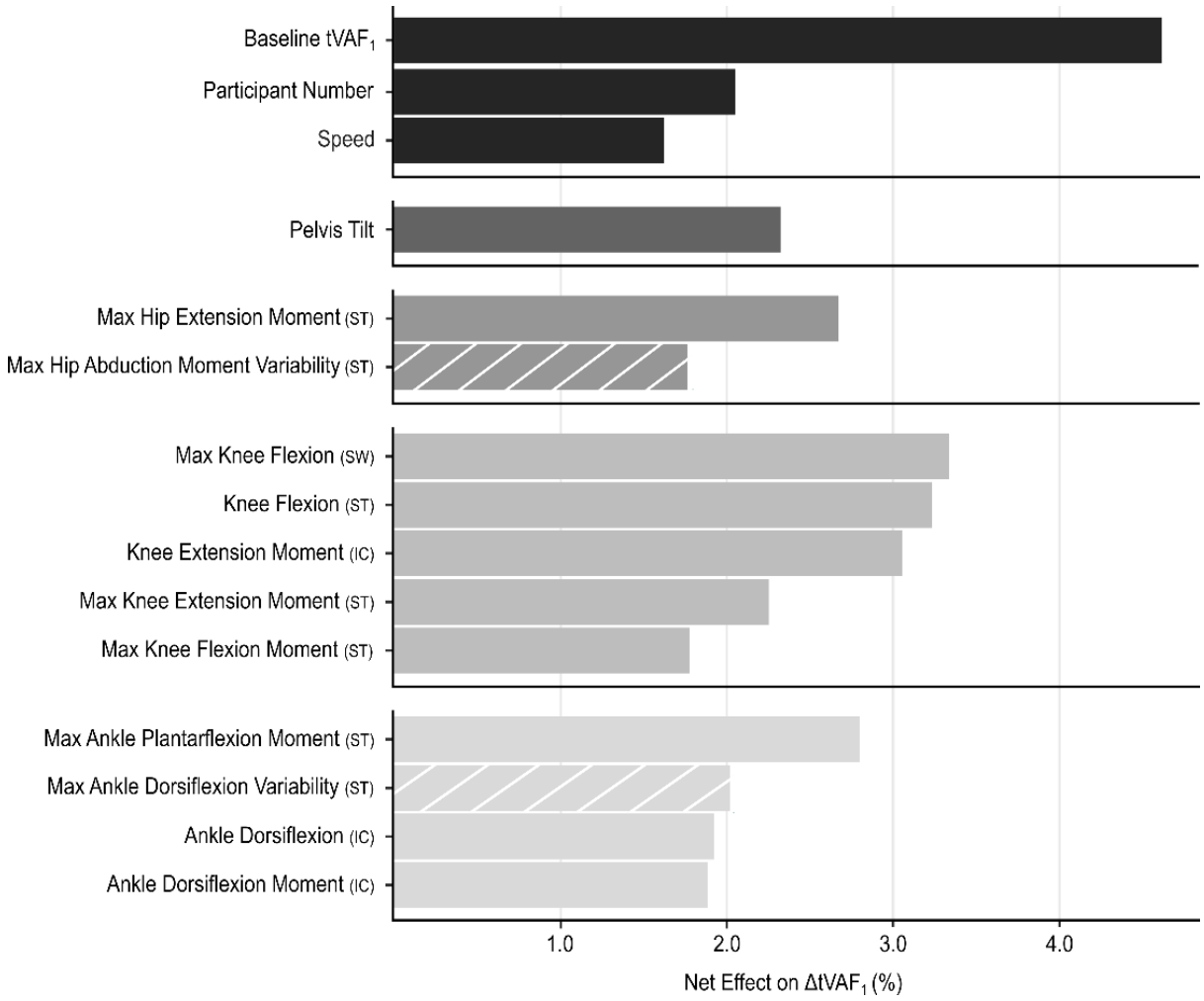

Figure 4.8 Net effects for the top fifteen input variables on ΔtVAF1 from the BART model. Net effects were derived from the generated ALE plots and defined as the difference between the 5th and 95th percentile of the response variable over the range of each input variable, when controlling for all other model covariates. Cross-hatching indicates measures of stride-to-stride variability. Gait phases: Initial contact (IC), stance (ST), and swing (SW). See Table 4.1 for all variables included in the BART model.

Beyond gait mechanics, both participant number (net effect = 2.1%) and speed (1.6%) emerged among the top input variables in the model. Although the former effect was largely driven by one participant (P8), it still indicates that differences may exist in how individuals interacted with the biofeedback system, including both the range of patterns they explored and their comprehension of the presented metric. Further, the moderate effect of speed on synergy complexity, whereby slower speeds were associated with greater decreases in complexity (Figure

4.9), could suggest differences in the feasibility of performing certain gait patterns at different speeds.

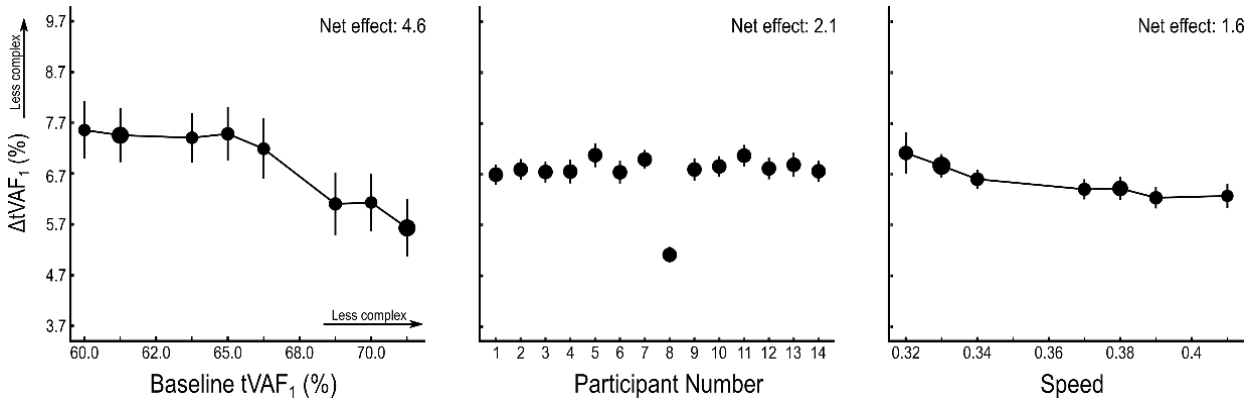

Figure 4.9 Accumulated local effect (ALE) plots for baseline synergy complexity, participant number, and speed. Speed is normalized to participant leg length. Each plot depicts the effect of an individual input variables on changes in synergy complexity from baseline, conditioned on all other covariates in the model. Input variable data is separated into evenly spaced bins and the size of individual points represents the number of samples in each bin. Larger values for $tVAF_1$ indicate less complex control. Net effects were calculated as the difference between the 95^{th} and 5^{th} percentile of $\Delta tVAF_1$ over the range of each input.

4.5 Discussion

This study demonstrated that a small library of synergies was sufficient to characterize a broad repertoire of gait patterns attempted during biofeedback walking, and that recruitment from this library was dependent on both the type and magnitude of gait pattern deviation. Specifically, small deviations from baseline walking were generally accommodated by altering the activations of a consistent set of synergies whereas different synergies were recruited to produce larger gait changes. Participants were also able to widely modulate synergy complexity during gait pattern exploration. However, the majority of gait patterns corresponded to an increase in $tVAF_1$ (*i.e.*, decreased complexity); across all participants, only 17.4% of attempted patterns decreased $tVAF_1$. Collectively, these results suggest that although synergy structures appear to be invariant, synergies can be flexibly recruited in response to changing sensory input or biomechanical

constraints. This organizational strategy is advantageous for enabling rapid learning of new movement patterns and ensuring successful navigation in complex environments[114,241,242].

Our observation that a small pool of synergies emerged during gait pattern exploration aligns closely with prior literature in both animal and human models. These studies have demonstrated that synergies are consistent across a repertoire of motor outputs[46,47,106,110,195] and can be flexibly combined to accommodate changes in sensory input[46,107,109,113,243] or biomechanical constraints[114,116,224]. However, beyond identifying differences in synergy recruitment across movements, the nature of our protocol enabled us to understand the factors associated with these differences with greater precision. For example, we demonstrated that small deviations at the hip, knee, and ankle, as observed in K_1, were accommodated by baseline synergies, as baseline synergy weights largely captured the variance in EMG activity during feedback walking (*i.e.*, $tVAF_{3\_BASE}$ for K_1). Baseline synergies were also recruited for the majority of patterns in K_5, as the large increase in knee flexion through swing could be accommodated by altering the activation timing of the hamstring synergy (W_2). In contrast, patterns which were defined by large deviations in sagittal plane mechanics through stance (*e.g.,* K_2 and K_4), had synergy structures more dissimilar from baseline (Figure 4.7). A similar relationship emerged when considering synergy complexity. The results from our BART analysis demonstrated that deviations at the knee and ankle during stance were strongly associated with changes in $tVAF_1$ during gait pattern exploration. Specifically, greater knee extension moment, ankle dorsiflexion moment, and knee flexion through stance corresponded to reduced complexity. This finding aligns with observations in clinical crouch gait in cerebral palsy, where a crouched posture places greater demand on the quadriceps to accelerate the center of mass upward and counteract gravitational force, resulting in increased coactivation of the hamstrings and quadriceps through stance and, therefore, reduced control

complexity[244,245]. Hip extension moment through stance also emerged among the top input variables in the BART model, which further indicates that increased hamstring-quadricep co-contraction had a large effect on $\Delta tVAF_1$.

Beyond identifying those variables which were most associated with changes in synergy recruitment, the results from the BART analysis also allowed us to capture the non-linear relationship between gait pattern deviations and synergy complexity. Specifically, a stepwise relationship consistently emerged for kinematic and kinetic input variables wherein $tVAF_1$ was similar to baseline values up until a certain threshold, after which changes in $tVAF_1$ were larger, but generally consistent. The stability of synergy complexity measures for gait patterns similar to baseline walking further confirms the propensity for the CNS to maintain a consistent control strategy to accommodate small gait deviations. Further, the plateau in $\Delta tVAF_1$ observed at the extremes of each gait variable suggest that bounds exist on the extent to which synergy complexity can be modulated, at least when limited to a specific muscle set.

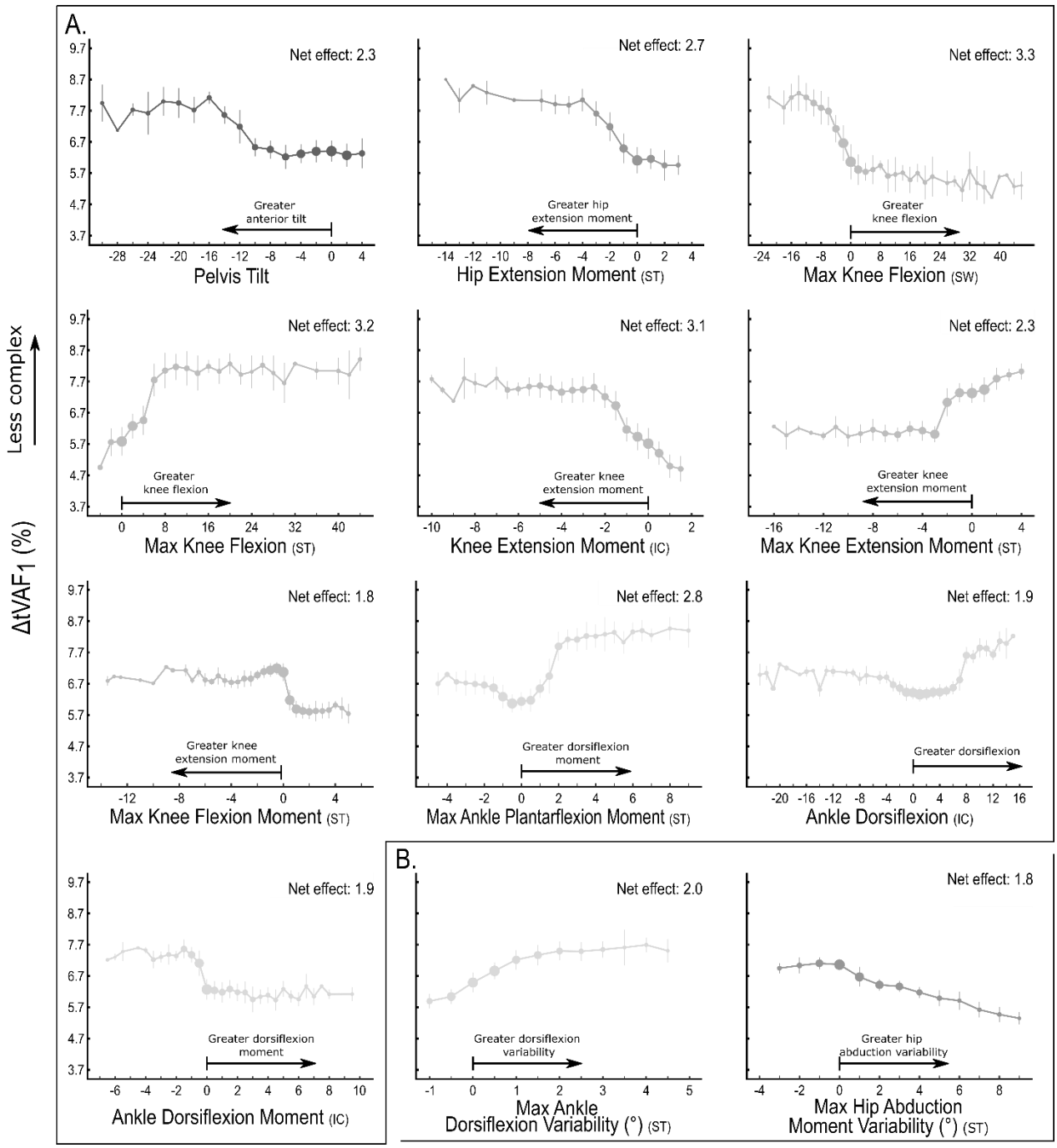

Figure 4.10 Accumulated local effects of kinematic, kinetic, and variability measures on $\Delta tVAF_1$. Kinematic and kinetic measures (A) are presented as z-scores normalized to baseline walking, such that the x-axis depicts standard deviations away from baseline. Variability measures (B) are presented as degrees away from baseline variability. Vertical bars indicate ± 1 SD. Plots are cropped to display the middle 95% of the input variable data to remove extreme outliers. Input variable data was separated into evenly spaced bins and the size of individual points represents the relative number of samples in each bin. Gait phases: Initial contact (IC), stance (ST), and swing (SW).

While outcomes from the BART analysis also revealed a monotonic relationship between baseline complexity and $\Delta tVAF_1$, partially reflecting regression to the mean, the overwhelming majority of patterns selected during exploration increased $tVAF_1$. Although these results could reflect participant comprehension of the biofeedback system and the task instructions, they may also be indicative of the underlying control strategy employed by the CNS during learning. In novel task execution, the CNS may initially assume a less complex strategy, sacrificing efficiency for stability. This hypothesis is consistent with studies demonstrating that long-term training facilitates more efficient use of neural resources[246,247] and increased supraspinal excitability[248–250]. For example, Sawers et al. (2015) demonstrated that trained dancers recruited a larger number of synergies than novices during both beam and overground walking and that the synergies recruited were sparser, both of which were used to suggest that training promoted greater selective motor control[124]. In our study, because individuals typically explored each gait pattern for a short bout (~10 strides) during exploration, the CNS may have had insufficient time to tune its control strategy, contributing to the observation that participants could increase, but not consistently decrease $tVAF_1$ values.

Whether synergy complexity is similarly flexible and can be consistently increased following neurologic injury is largely unknown but is especially salient for informing gait rehabilitation. Individuals with central nervous system damage recruit fewer synergies than nondisabled peers[38,117–121]. Further, within these populations, both synergy complexity and structure have been associated with impairment level, as those with more severe impairments have less complex control[38,118]. This is hypothesized to reflect increased reliance on spinal circuitry over supraspinal input to shape motor outputs following neurologic injury, which may reduce the overall flexibility of synergy recruitment[37]. This relationship has been demonstrated in CP, where

prior literature has reported that synergies are unchanged following surgery and biofeedback training, despite both interventions yielding measurable improvements in gait[34,35]. Further, stroke survivors with less severe impairment appear to maintain the capacity to modulate synergies during locomotor training better than those with more severe impairment[217]. Understanding whether individuals with neurologic injury can consistently alter synergy complexity and improve movement, or how interventions can support sustained changes in control remain active and important areas for future investigations. While recent literature has indicated that providing richer afferent information via spinal stimulation or sensorimotor biofeedback may promote greater supraspinal involvement and, therefore, more flexible synergy recruitment during movement, studies are still ongoing[40,128,251].

Finally, our observation that participant number was associated with $\Delta tVAF_1$ further accentuates the need to evaluate personalized responses to biofeedback. This result suggests that even when controlling for all other model covariates, including baseline complexity, interparticipant differences in response persisted. Heterogeneous response to biofeedback training has been cited previously and may stem from both individual capacity to modify the parameter targeted by biofeedback as well as system design choices[21,22,34,134,142,252]. The latter likely contributed to the results observed here. Because synergy complexity is derived from multiple data streams, some participants reported feeling unsure about how specific gait changes affected the displayed metric or struggled to conceptualize what 'more' or 'less' complex gait patterns entailed, both of which likely influenced their exploration strategy. These results highlight an inherent challenge of using motor control-based biofeedback in gait training applications and present an opportunity to explore more interpretable biofeedback metrics that can still be used to improve control patterns. For example, the output from our model suggests that providing information on

joint moments to reduce hamstring-quadricep co-contraction in early stance may elicit changes in synergy complexity, although further work is needed to extend these findings to populations with neurologic injury. Our results also demonstrate the unique advantage of using non-linear function estimation techniques such as BART in order to better interpret the inherently complex and multifactorial user-system interactions present during biofeedback training to inform future system design.

4.5.1 Methodological Considerations

Although the decision to use a biofeedback system and minimal researcher coaching allowed us to capture a broader array of patterns than have been previously examined in studies of synergies in gait, there are limitations to this approach that should be considered when interpreting the results. Because we wanted participants to freely explore using the biofeedback system, we only required them to take five strides in a selected gait pattern. This meant that the novelty of the attempted patterns was likely reflected in our results, as previously described. In order to reduce this effect, we calculated synergies from the same number of strides during exploration and baseline walking (n = 5); however, it is possible that synergies may have adapted further if we had collected a larger number of strides for each pattern[210]. The unstructured nature of the protocol also introduced the likelihood of observing extreme outliers, as a given gait pattern may only be attempted by a single participant. The opportunity for outliers and observed heterogeneity of participant response informed our decision to use BART as a modeling paradigm. Because BART natively constrains tree structure, it prevents data overfitting, thereby reducing the likelihood that outliers in our data set could significantly affect model outputs[233]. Further, the choice to use a sliding five-stride window of EMG data for the synergy complexity calculation, while improving the stride-to-stride stability of the feedback metric, meant that the system may not be immediately

responsive to single-stride gait changes. While we attempted to mitigate this effect by instructing participants to take at least five strides in each selected gait pattern, this design decision may have influenced how participants understood and interacted with the biofeedback system.

Our analysis was also restricted to small muscle set on the dominant leg, which introduced additional limitations. While the muscle set we selected aligns with those commonly used it clinical gait analysis[122,253], it predominantly characterized sagittal plane motion, despite the fact that most of the gait pattern attempted had deviations in all three planes (Figure 4.4). As such, the BART model identified sagittal plane variables as having the largest net effect on $\Delta tVAF_1$ and, therefore, limited the conclusions that could be drawn about how frontal and transverse plane mechanics impact synergy recruitment. We also focused on our analysis on the dominant limb, given our unilateral feedback system. However, as walking inherently requires interlimb coordination, characterizing synergies bilaterally and understanding the extent to which asymmetric gait pattern exploration affects synergy recruitment is a critical area for future research.

Despite the diversity of patterns attempted, our analysis was still also limited to a subset of gait patterns making it challenging to draw definitive conclusions about the relationship between biomechanical constraints and synergies. In future studies, biofeedback systems may be useful to guide users through a sample of possible walking configurations in order to develop a more comprehensive landscape of user response. Simulation paradigms, such as those employed by Kutch and Valero-Cuevas (2012), which involve systematically iterating over a range of achievable outputs, could also be a valuable compliment to the present study to provide further insight into how synergies change as a function of gait exploration[42]. Importantly, such analyses

need to be performed in both nondisabled populations and those with neurologic injury in order to understand how injury impacts one's ability to flexibly alter control strategies during walking.

4.6 Conclusion

Using motor control-based biofeedback to encourage gait pattern exploration and capitalizing on non-linear machine learning methodology allowed us to identify salient features which influence how the CNS flexibly shapes control during walking. This analysis revealed that a small library of spatially invariant synergies can be flexibly recruited to produce a diverse array of motor outputs and that recruitment changes as a function of the imposed biomechanical constraints. Specifically, our results suggest that large deviations in distal joint mechanics during stance resulted in the greatest overall change in synergy recruitment from baseline walking. They also indicate that other participant-level factors may affect one's ability to modify synergy recruitment during walking, which must be considered when designing interventions to this end. Whether the recruitment flexibility observed in this study is a luxury of the unimpaired neurological system or is maintained following neurological injury is a critical next step of this work. Similarly, understanding whether the capacity to modulate synergies changes as a function of central nervous system maturation will help shape the development of novel rehabilitation strategies and inform intervention timelines. By modeling how synergies are modulated during locomotion, we believe that this study presents both theoretical and methodological contributions towards bolstering understanding of the neural control of movement and may aid in improving interventions for individuals with neurological injury.

Chapter 5

AUDIOVISUAL BIOFEEDBACK AMPLIFIES PLANTARFLEXOR ADAPTATION DURING WALKING IN CHILDREN WITH CEREBRAL PALSY

In preparation

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ABSTRACT

Background: Biofeedback is a promising non-invasive strategy to enhance gait training among individuals with cerebral palsy (CP). Commonly, biofeedback systems are designed to guide movement correction using audio, visual, or sensorimotor (*i.e.*, tactile or proprioceptive) cues, each of which has demonstrated measurable success in CP. However, it is currently unclear how the modality of biofeedback may influence user response, which has significant implications if systems are to be consistently adopted into clinical care.

Methods: In this study, we evaluated the extent to which adolescents with CP (7M/1F; 14 years [12.5,15.26]) adapted their gait patterns during treadmill walking (6 min/modality) with audiovisual (AV), sensorimotor (SM), or combined AV + SM biofeedback before and after four acclimation sessions (20 min/session) with both systems. Both biofeedback systems were designed to target plantarflexor activity on the more-affected side, as these muscles are commonly impaired in CP and impact walking function. SM biofeedback was administered using a resistive ankle exoskeleton and AV biofeedback indicated soleus activity during gait. At each visit, we measured the time-course response to each modality of biofeedback to understand how the rate and magnitude of gait adaptations differed between biofeedback modalities and following acclimation to both systems.

Results: Participants significantly increased soleus activity from baseline using AV + SM (42.8% [15.1, 59.6]), AV (28.5% [9.2, 58.5]), and SM (10.3% [3.2, 15.2]) biofeedback. However, participants adapted soleus activity more quickly in response to AV + SM biofeedback, than either modality alone, suggesting combined biofeedback amplified user response. Further, SM-only biofeedback produced small initial increases in plantarflexor activity, but responses to this modality were not maintained within or across sessions ($p = 0.195$). Following multi-session

acclimation and at a two-week follow-up, the rate and magnitude of response to AV and AV + SM biofeedback were maintained.

Conclusions: This study demonstrated that AV biofeedback was critical to increase plantarflexor engagement during walking, but that combining multiple biofeedback modalities further increased the rate of gait modification. Beyond improving understanding of how individuals may differentially prioritize distinct forms of afferent information, outcomes from this study highlight the relative advantages of distinct modalities of biofeedback which can inform the development and selection of systems for use in clinical care.

5.1 INTRODUCTION

Mobility is critical for promoting independence and facilitating broad social, emotional, and cognitive development[1–3]. However, for individuals with cerebral palsy (CP), a non-progressive neurologic injury in early development affects coordination and can lead to a variety of progressive secondary impairments which may restrict walking capacity over time[6,254]. To improve mobility, individuals with CP commonly participate in treadmill-based gait training, which is designed to provide task-specific and high-intensity practice[4,23,25,70]. While treadmill training has demonstrated success in CP[10,70,129], traditional protocols require high levels of therapist coaching in order for individuals to consistently recognize and correct movement error[70]. This not only increases the burden on therapists for longer training sessions, but may attenuate response, as treatment goals may be vague or inconsistently reinforced[70].

Biofeedback is a promising extension of treadmill training, as it enables *self-initiated* error correction during *goal-directed* practice[22]. Biofeedback systems are designed to provide the user with real-time information on a specific gait parameter (*e.g.,* joint angle, force, movement accuracy, muscle activity) in relation to a desired performance to augment existing intrinsic (*i.e.*, tactile or proprioceptive) pathways and enhance error recognition[22,49,134]. Commonly, systems are designed to present information visually, via displays or immersive environments, or aurally, using tones or music. Such biofeedback systems (collectively termed audiovisual (AV) biofeedback) have been used successfully to improve spatiotemporal parameters[21,31,33,255], joint power[30], joint kinematics[21], and muscle activity[144] in individuals with CP. More recently, sensorimotor (SM) biofeedback systems, such as exoskeletons[27,39,256,257] or vibrotactile arrays[258], have been developed as a means of directly interfacing with intrinsic feedback pathways during walking to provide critical temporal and spatial information; this approach may be particularly valuable in CP where

sensory processing is commonly impaired[6,50]. To this end, Conner and colleagues recently demonstrated that providing SM biofeedback using a resistive ankle exoskeleton during walking elicited improvements in energy expenditure[27], walking speed[27], and motor control[40] in a CP cohort.

While the demonstrated success of these studies highlights the potential of using biofeedback in CP rehabilitation, combining modalities may further amplify outcomes[134]. Robust error recognition drives adaptation to perturbation, which suggests that presenting simultaneous extrinsic and intrinsic information using biofeedback may elicit greater adaptation and, therefore, increase the magnitude of responses[158,185,191]. This aligns with the theory of multisensory integration which states that providing information across disparate sensory pathways may induce a faster and more accurate response than unisensory stimuli and help to prevent cognitive overload, particularly for complex tasks[134,151,259,260]. Further, training with multisensory systems has been hypothesized to strengthen the connections between sensory areas and enhance future unisensory retrieval[134,151]; practically, this means that individuals who train with multimodal biofeedback may be able to transition to simpler systems for longer-term reinforcement. These hypothesized benefits of multimodal over unimodal biofeedback during walking have been explicitly evaluated in nondisabled[147] stroke[149], and spinal cord injury populations[139]. However, in CP, there is still limited understanding of how the choice of biofeedback modality influences responses and, importantly, if there are advantages to presenting multimodal biofeedback during gait training[49,256,261].

The aim of this study was to evaluate the extent to which individuals with CP adapt their gait patterns using AV and SM biofeedback, presented independently and in combination. Secondarily, we evaluated if response was retained or further enhanced immediately and two-weeks following multi-session acclimation to both systems. We hypothesized that individuals with

CP would be able to modify their gait patterns in response to each biofeedback modality, but that presenting AV and SM biofeedback in parallel would promote greater error recognition and, therefore, increase both the magnitude and rate of response compared to either modality alone. Secondarily, we hypothesized that following multi-session acclimation, participants would adapt gait more quickly and to a greater magnitude while using all modalities, suggesting they had retained knowledge of the biofeedback systems. As different biofeedback modalities may be more or less translatable to clinical environments, due to cost or other constraints, results from this study will help to guide decision making regarding the selection and addition of biofeedback into gait training for individuals with CP[49,261,262].

5.2 METHODS

5.2.1 Participants

Eight individuals with CP were recruited to evaluate adaptation to multimodal biofeedback (see Table 5.1 for participant demographics). Prior to participation, informed consent was provided by participants and their caregivers, and the study protocol was reviewed and approved by the Northern Arizona Institutional Review Board. Individuals were eligible for participation if they had: (1) the ability to walk for ten minutes on a treadmill, using handrails as necessary, (2) the ability to follow verbal instructions and respond to audio and visual cues, (3) no history of orthopedic surgery or lower-limb botulinum toxin injections within the last six months or had received clinician approval that any recent interventions had minimal effects on gait, and (4) no other conditions that would make participation unsafe, decided at the discretion of the research team.

Table 5.1 Participant Demographics

	Gender	GMFCS Level[a]	Diagnosis[b]	Age (yrs)	Height (m)	Mass (kg)	More-Affected Limb[c]	Walking Speed (nd)[d]
P1	M	II	SD	18	1.76	62.14	R	0.31
P2	M	II	SD	12	1.45	42.41	L	0.28
P3	F	III	SD	13	1.58	42.18	R	0.22
P4	M	II	SD	15	1.65	60.78	L	0.25
P5	M	II	SD	13	1.50	39.01	R	0.31
P6	M	I	SH	12	1.43	39.46	R	0.32
P7	M	III	SD	15	1.56	68.95	L	0.23
P8	M	I	SH	16	1.65	65.77	R	0.27

[a]Gross Motor Function Classification System; Level determined by licensed physical therapist
[b]Diagnoses include: Spastic diplegia (SD), spastic hemiplegia (SH); Diagnosis reported by participant caregivers
[c]Reported by participants
[d]Nondimensional, calculated according to Hof A.L., 1996

5.2.2 Experimental Protocol

All participants walked on a treadmill under three biofeedback conditions: (1) SM only, (2) AV only, and (3) combined AV + SM (Figure 5.1). Both modalities were designed to directly target soleus activity on the more affected limb, as reported by the participant (see Section 5.2.3 and 5.2.4 for full system details). The plantarflexors were selected for this application, as they are critical for forward propulsion and commonly affected in CP[254,263]. Further, providing biofeedback on muscle activity, rather than gait mechanics, is a marked deviation from most existing paradigms in CP, but may be more effective for eliciting changes higher up in the motor control hierarchy[49].

Each trial was structured to include baseline (1 minute), feedback (6 minutes), and washout (1 minutes) phases and trials were separated by mandatory 5-minute seated breaks. During the feedback phase, participants were instructed to hold onto the handrails with both hands for safety. During both baseline and washout phases, the biofeedback systems were turned off and participants were instructed to walk in whatever way felt natural. This washout phase was included to capture any aftereffects, which can provide insight into the extent of carry-over of the adapted gait pattern[152]. Given the short duration of walking with biofeedback, this protocol was not

designed to evaluate training effects without biofeedback, but rather to evaluate how biofeedback can support desired responses during treadmill-based training.

We evaluated participant response to each biofeedback modality across three visits (Figure 5.1). Between visit one (pre-acclimation) and visit two (post-acclimation), participants performed four, 20-minute acclimation sessions with both biofeedback systems. Visit three (follow-up) was performed after two-weeks without exposure to either biofeedback system to evaluate retention of responses to each modality. During the pre-acclimation visit, a licensed physical therapist confirmed the participant's self-reported Gross Motor Function Classification System (GMFCS) level, more-affected limb, and evaluated knee (flexion/extension) and ankle (dorsi/plantarflexion) range-of-motion and spasticity, the latter of which was quantified using the Modified Ashworth Scale[264] (0: no spasticity, 4: limb rigidity). Across all visits, participants walked at a consistent self-selected speed (Table 5.1) and the order of modalities was pseudo-randomized to control for fatigue and learning effects.

5.2.3 Sensorimotor Biofeedback

Sensorimotor biofeedback (SM) was administered using a lightweight, battery-powered ankle exoskeleton, that has been previously used in CP[27,39,257,265,266]. Briefly, this system uses DC motors, worn on a hip belt, to drive Bowden cables which actuate bilateral ankle assemblies (Figure 5.1). The ankle assemblies include carbon fiber calf-cuffs and foot plates that can be sized to the individual to ensure optimal device fit. Force sensitive resistors, embedded in the footplates under the metatarsal heads, provide an on-board controller with a real-time estimate of the biological ankle moment and gait phase which are used to set the magnitude of the applied torque. During a baseline walking trial, the system is calibrated such that participants will receive a nominal torque value if their estimated biological ankle moment is similar in magnitude to baseline values and

receive proportionally higher or lower torque values otherwise; this design ensures that the device adapts to user input for every stride[39,266,267]. A custom Matlab interface communicates with the device via Bluetooth, enabling researchers to change the nominal torque value for both limbs and monitor system performance in-trial.

For the SM and AV + SM trials, the device was used to impart a *resistive* (*i.e.*, dorsiflexion) moment at push-off on the more affected limb to promote plantarflexor recruitment. Across all three visits, the nominal resistive torque was set at 0.15 Nm/kg and 0 Nm/kg, normalized to participant mass, on the more-affected and less-affected limbs, respectively; the 'zero-torque' mode imposed on the less-affected side, effectively turned the ankle assembly into a hinge joint. During the baseline and washout phases, the same zero-torque mode was applied to the more-affected limb so as to capture the immediate transition between biofeedback and no-biofeedback walking without needing to stop the treadmill and doff the device. In the four acclimation sessions, held between the pre-acclimation and post-acclimation visits, torque was applied bilaterally, and the nominal torque value was incrementally adjusted from 0.1 Nm/kg to 0.2 Nm/kg to maintain task challenge.

We elected to use a resistive exoskeleton paradigm to administer SM biofeedback because we believe that it has a unique advantage over assistive devices, which are commonly used to the same ends[256,266,268,269]. We hypothesized that the imposed resistive torque about the ankle would not only provide feedback on appropriate muscle activation timing, but it would amplify existing movement error and thereby accelerate adaptation[153,165,191,270]. Further, the paradigm may also be particularly advantageous for translation into rehabilitation, as it encourages rather than supplants biological plantarflexor activity, promoting functional strength training and discouraging user 'slacking'[132].

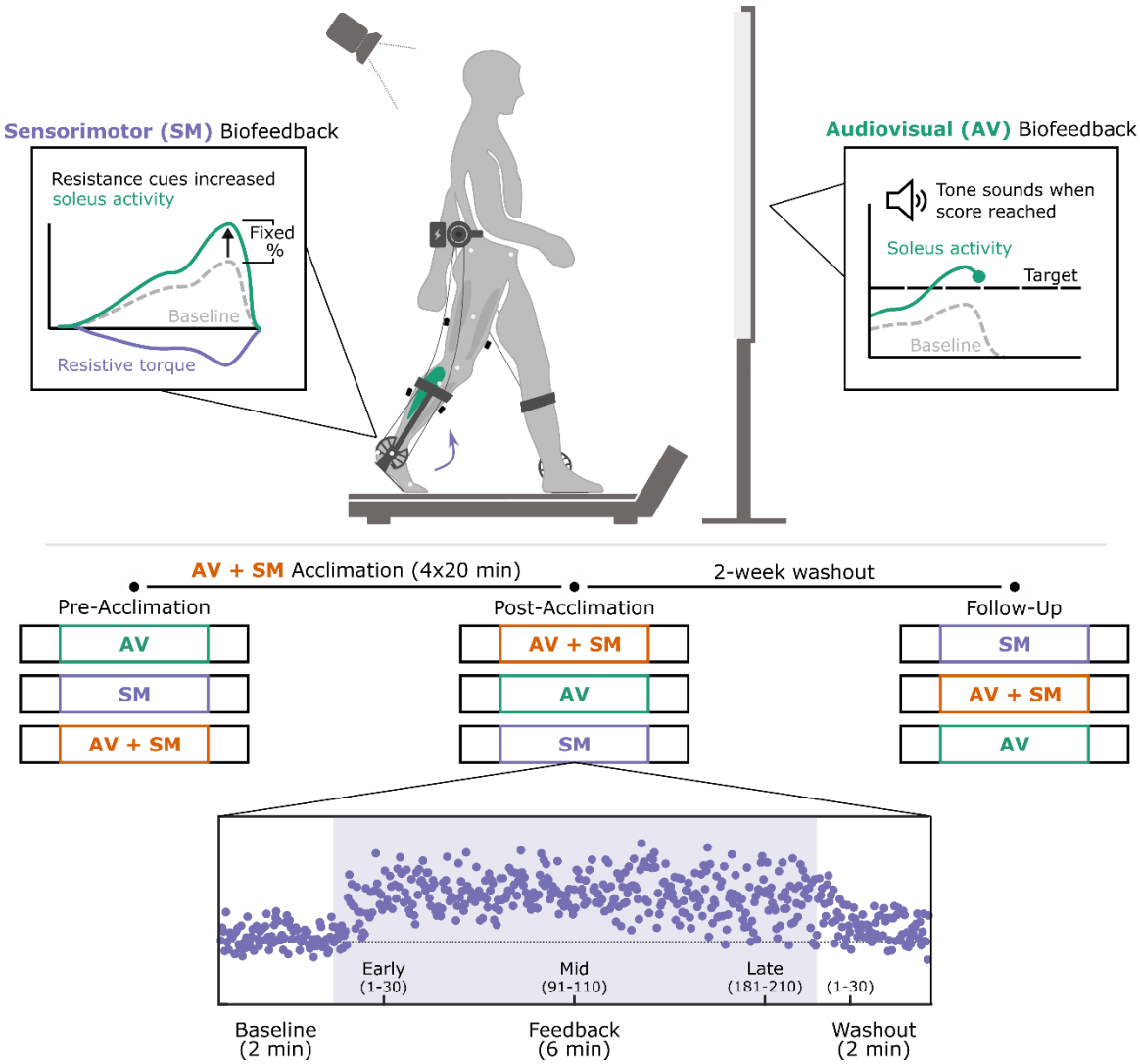

Figure 5.1 Experimental Protocol. Audiovisual (AV) biofeedback on soleus activity was provided for the more-affected leg alongside an auto-adjusting target score. Sensorimotor (SM) biofeedback was applied on the more-affected leg using an untethered ankle exoskeleton that is designed to impart a resistive ankle torque through stance, proportional to baseline values. Participants completed three data collection visits (pre-acclimation, post-acclimation, and follow-up), during which they walked with both biofeedback systems independently and in combination, presented in a pseudo-randomized order. Each trial was 10 minutes and separated into baseline, feedback, and washout phases. All data analysis was performed for early (strides 1-30), mid (strides 91-110), and late (strides 181-210) feedback phases and washout (strides 1-30).

5.2.4 Audiovisual biofeedback

The audiovisual (AV) biofeedback system was custom designed in Matlab (Mathworks; Natick, MA). This system streamed real-time electromyography (EMG) data from the soleus on the more-affected limb using Vicon Datastream (Denver, CO). These data were then smoothed using an 80

ms moving average filter and presented back to the user on a simple graphical display (Figure 5.1) alongside a target score. Each time the target score was reached a tone sounded to notify the participant of a successful activation. To maintain task challenge and participant motivation, the target score was designed to be programmatically adjusted to keep user success rate between 50 – 75%, based on a sliding 10-stride window; if the participant's success rate fell outside of these bounds (*e.g.*, they reached the target score in only four of the last ten strides), the target score would be either raised or lowered by 10%. This adaptive controller design not only ensured congruency with the adaptive SM system, but aligns with the challenge point framework, which hypothesizes that motor learning can be negatively impacted if task difficulty is too high, particularly for novice users[271].

5.2.5 Data Analysis

Across all three visits, surface EMG data were recorded bilaterally from the tibialis anterior, soleus, vastus lateralis, and semitendinosus, which were placed according to SENIAM guidelines (Noraxon; Scottsdale, AZ; 1000 Hz). EMG data were low-pass filtered (40 Hz; 4th order Butterworth), rectified, and high-pass filtered (10 Hz; 4th order Butterworth). A robust-PCA algorithm was then applied to the linear envelopes to remove any non-physiological signal spikes due to sensor movement and data was normalized to the 95th percentile of the first baseline phase evaluated[207,209]. In parallel, lower-limb motion data were collected using a 10-camera motion capture system and the Vicon Lower Limb Plug-in Gait marker set (Denver, CO; 100 Hz; Figure 5.1). Three-dimensional joint kinematics were then derived from marker data using the Vicon Plug-In Gait dynamic pipeline. Secondarily, spatiotemporal parameters (*e.g.*, stride length, stride width, step length) were calculated from marker data using the Gait Cycle Parameter Calculator in Vicon ProCalc. All EMG, kinematic, and spatiotemporal data were segmented into individual

strides using the fore-aft heel marker and toe marker positions to determine heel-strike and toe-off, respectively.

Because participants may make bilateral modifications to the imposed unilateral perturbation, we characterized both intralimb and interlimb mechanics during each visit. Intralimb mechanics were defined as changes in (1) mean muscle activity, (2) co-contraction, (3) stride length, and (4) joint angles compared to baseline walking. Co-contraction was quantified for the soleus (SOL) and tibialis anterior (TA) using the co-contraction index (CCI)[272]:

$$CCI = \frac{2 * \int_1^t Min(TA_t, SOL_t)}{\int_1^t TA_t + \int_1^t SOL_t} \tag{5.1}$$

which measures the extent to which the integrated area of EMG data for both muscles overlaps across the gait cycle (t = 100 time points).

Interlimb mechanics were evaluated using step width and step length asymmetry measures. Step width was quantified as the medio-lateral difference between heel strikes on opposing limbs. Step length asymmetry was calculated as:

$$SLA_{targeted} = \frac{SL_{targeted} - SL_{nontargeted}}{SL_{targeted} + SL_{nontargeted}} \tag{5.2}$$

which captures step length differences between the limb with ($SL_{targeted}$) and without ($SL_{nontargeted}$) biofeedback[190] where step length is defined as the fore-aft difference between consecutive heel strikes on the same limb.

5.2.6 Statistical Analysis

To characterize transient responses to each biofeedback modality, we evaluated all metrics at three instances within the biofeedback walking phase - early adaptation (strides 1-30), mid adaptation

(strides 91-110), and late adaptation (strides 180-210) – as well as early washout (strides 1-30; Figure 5.1). While some participants took more than 210 strides during the biofeedback phase, we elected to match stride numbers across all participants to control for the effect that repetition may have on learning. For each participant, all interlimb and intralimb parameters were normalized to the first baseline phase evaluated for each visit.

We compared changes in interlimb and intralimb mechanics from baseline for each modality at each phase of biofeedback walking (*i.e.*, early, mid, and late), using multiple Wilcoxon signed rank tests. Secondarily, we compared if interlimb and intralimb mechanics differed significantly between biofeedback modalities for each phase using multiple Kruskal-Wallis tests. For those tests that reached significance, post-hoc Wilcoxon signed ranks tests were used to perform pairwise comparisons. All comparisons to baseline walking and post-hoc tests were adjusted using a Holm-Šídák correction to account for multiple comparisons ($n = 3$). Across tests, significance was set at $p < \alpha$ for $\alpha = 0.05$. All statistical analyses were performed with the Matlab Statistical Toolbox (MathWorks, Natick, USA).

5.3 Results

5.3.1 Pre-Acclimation Response

When biofeedback was first turned on, participants were able to significantly increase mean soleus activity from baseline walking with each modality (Figure 5.2; $p = 0.023$). However, the magnitude of changes in soleus activity with AV (median [IQR]: 28.5% [19.2,58.5]) and AV + SM (42.8% [15.1,59.6]) biofeedback were more than two times that of SM biofeedback alone (10.3% [3.2,15.2]). Further, while participants were able to maintain elevated soleus activity across the entire biofeedback session using AV (late phase: 23.9% [15.4,35.2]) and AV + SM (late phase:

21.9% [12.4,41.3]) modalities, response to SM biofeedback was transient, returning to baseline by mid-session ($p = 0.195$).

There was no statistical difference in the magnitude of mean soleus activity between AV and AV + SM biofeedback during the early, mid, and late phases of the pre-acclimation visit ($p > 0.640$), which suggests limited additive advantage of combining modalities. However, when examining early adaptation, individuals adapted more quickly to AV + SM biofeedback compared to the AV-only modality (Figure 5.3). Within the first five strides of the biofeedback systems being turned on, participants increased soleus activity from baseline by 36.5% [8.2,78.1] using AV + SM ($p = 0.046$), whereas response to SM and AV biofeedback was not significantly different from baseline at the same point ($p > 0.106$).

Despite the observed in-session gains for each modality, soleus activity rapidly returned to baseline once the systems were turned off, indicating that there was limited short-term retention of the adapted gait patterns ($p > 0.38$ for all modalities during washout). In-session gains were also largely unilateral, as soleus activity was similar to baseline in the non-targeted limb (*i.e.,* less-affected limb) across all modalities and phases of biofeedback walking ($p > 0.09$).

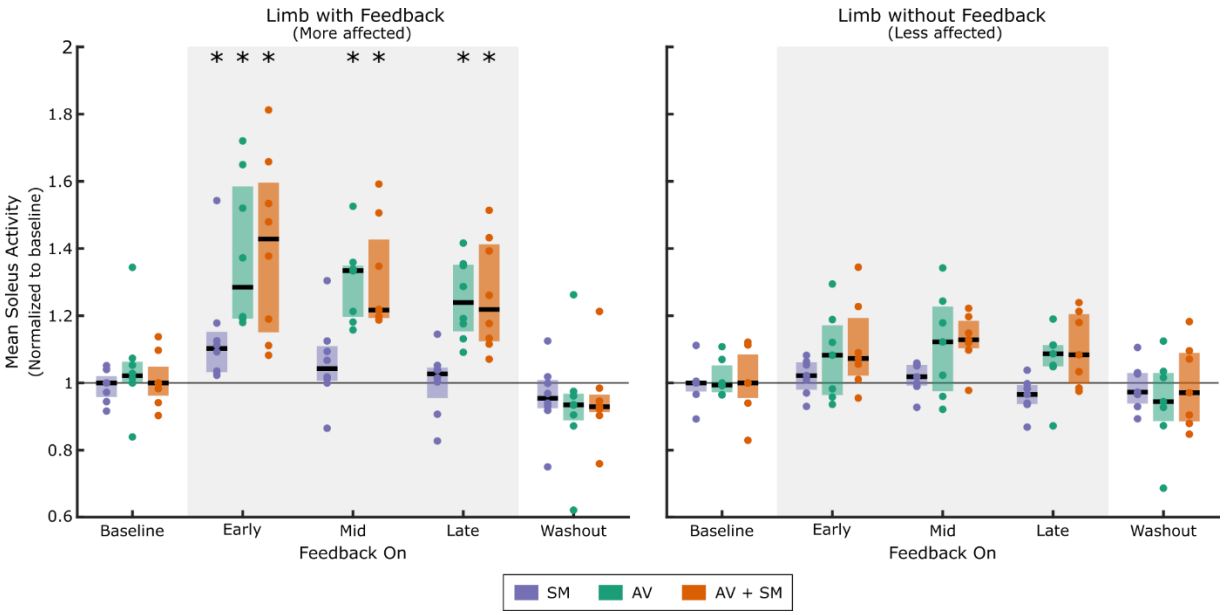

*Figure 5.2 Mean soleus activity for the more affected (left) and less affected (right) limb during walking with sensorimotor (SM), audiovisual (AV) and combined (SM + AV) biofeedback at the pre-acclimation visit. Biofeedback was provided unilaterally on the more affected limb. All data has been normalized to the first baseline walking period attempted. For each participant, mean soleus activity during early (strides 1-30), mid (strides 91-110), and late (strides 180-210) adaptation and washout (strides 1-30) was calculated and represented as individual dots. Boxes plots display the median (IQR) response. During both washout and baseline periods, the biofeedback systems were turned off. *indicates a statistical difference in soleus activity from baseline walking (Wilcoxon signed-rank tests with Holm-Šídák correction; $p < 0.05$).*

Although both modalities were designed to directly target soleus activity, participants altered their multi-muscle control strategy with biofeedback. The CCI between the tibialis anterior and soleus did not change significantly from baseline walking for any biofeedback modality ($p > 0.68$). However, vastus lateralis activity was elevated from baseline during early adaptation across all modalities (SM: 5.4% [1.8,42.2]; AV: 43.7% [14.3,61.1]; AV + SM: 70.5% [36.4,85.5]) and remained elevated with AV + SM biofeedback across the entire feedback-on phase (Figure 5.4). Semitendinosus activity was also elevated during early adaptation to AV + SM biofeedback (57.6% [3.6, 100.1]). Taken together, this suggests that individuals were adopting proximal compensations, particularly with AV + SM biofeedback, to modulate soleus activity. Note that two

participants were not included in this analysis, due to EMG signal losses during one session (vastus lateralis sensor for P3 at follow-up and P6 at pre-acclimation).

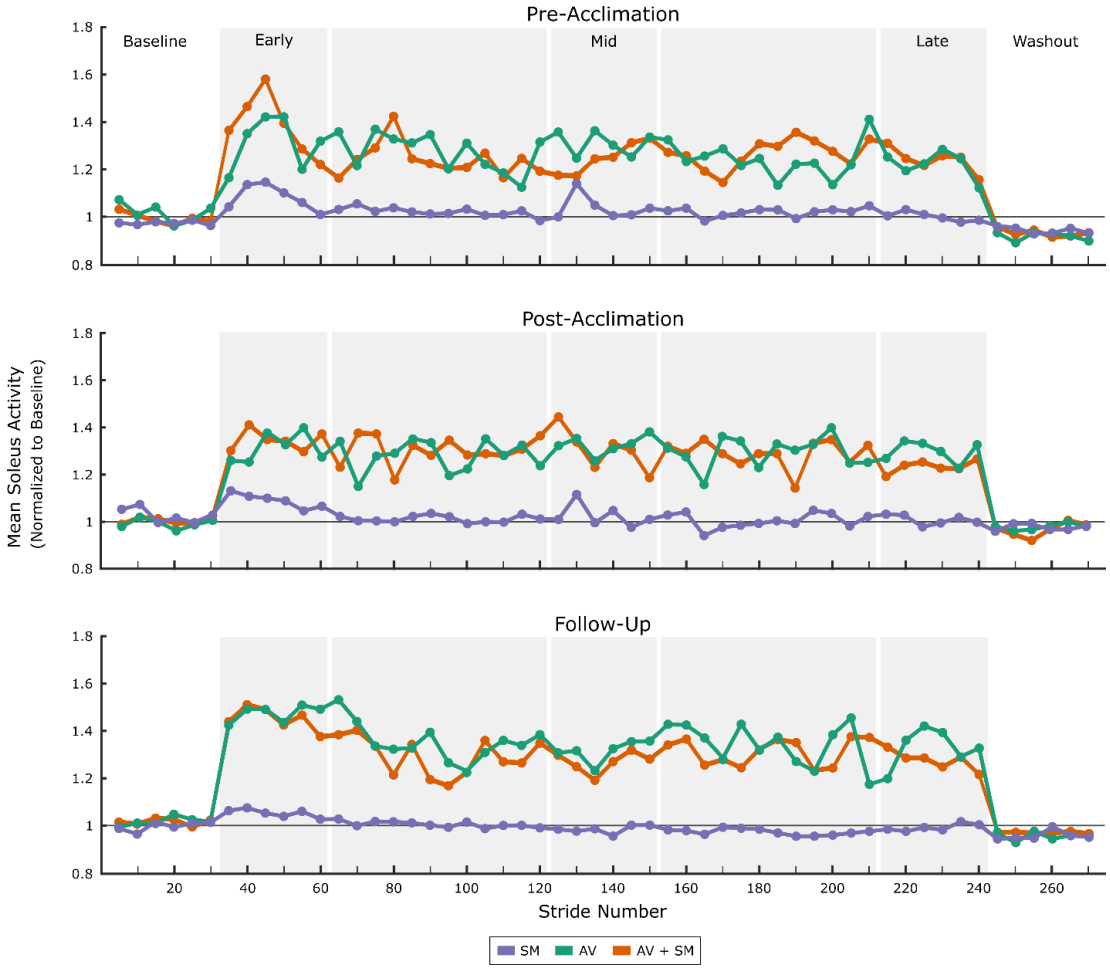

Figure 5.3 Time-course change in mean soleus activity for the more-affected limb during walking with sensorimotor (SM), audiovisual (AV), and combined biofeedback before and after four acclimation sessions with AV + SM biofeedback and after a two-week follow-up. All data has been normalized to the first baseline phase performed at each visit and averaged into 5-stride bins. During baseline and washout phases, the biofeedback systems were turned off.

While muscle activity was significantly modified during biofeedback walking, there were minimal changes in spatiotemporal parameters (Figure 5.5). In general, participants increased stride length on the more affected side and decreased step width with biofeedback, although there were not significant differences between modalities ($p > 0.47$ across all phases and modalities). There was also a small, but non-significant decrease in step length asymmetry towards zero when

walking with biofeedback compared to baseline, particularly with the AV + SM modality (SLA: 0.006 [-0.2,16.8]; p = 0.38).

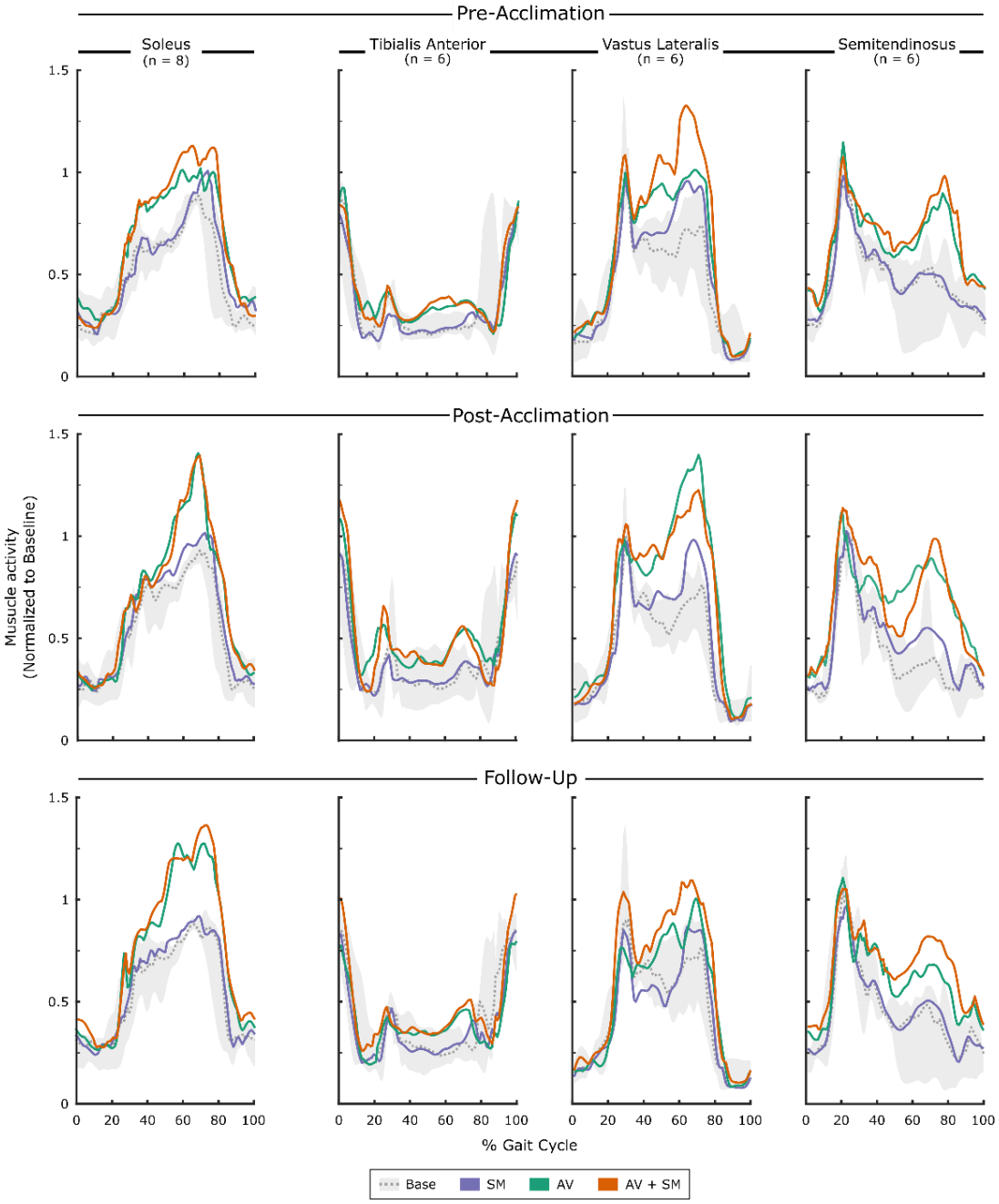

Figure 5.4 Muscle activity across all participants during early adaptation (strides 1-30) to sensorimotor (SM), audiovisual (AV), and combined (AV + SM) biofeedback in the pre-acclimation (top), post-acclimation (middle), and follow-up (bottom) visits. For each visit, data was normalized to the 95th percentile of each participant's first baseline phase. Baseline trends display median (IQR). Note that the trends shown for the tibialis anterior, vastus lateralis, and

semitendinosus represent six of the eight participants tested, as two had to be removed due to loss of vastus lateralis signal during collection.

In contrast to spatiotemporal parameters, participants altered kinematics in response to biofeedback (Figure 5.6). Participants significantly increased hip flexion at initial contact during walking with AV and AV + SM modalities ($p < 0.046$) compared to baseline. Knee flexion at initial contact also increased for both modalities, but changes did not reach significance ($p > 0.11$). During swing, participants significantly increased knee and hip flexion from baseline with AV biofeedback ($p < 0.046$) and knee flexion with AV + SM biofeedback ($p = 0.031$). The largest discrepancy between AV + SM and AV modalities was seen at the ankle; SM and AV + SM biofeedback yielded significant increases in ankle dorsiflexion ($p < 0.023$), whereas there were small but nonsignificant decreases in dorsiflexion with AV biofeedback ($p > 0.21$). Plantarflexion during push-off was also greater with AV biofeedback than either SM or AV + SM modalities (Kruskal-Wallis; $p < 0.023$ for mid and late phases). No significant differences in pelvic kinematics or hip abduction were observed for any biofeedback modality ($p > 0.11$).

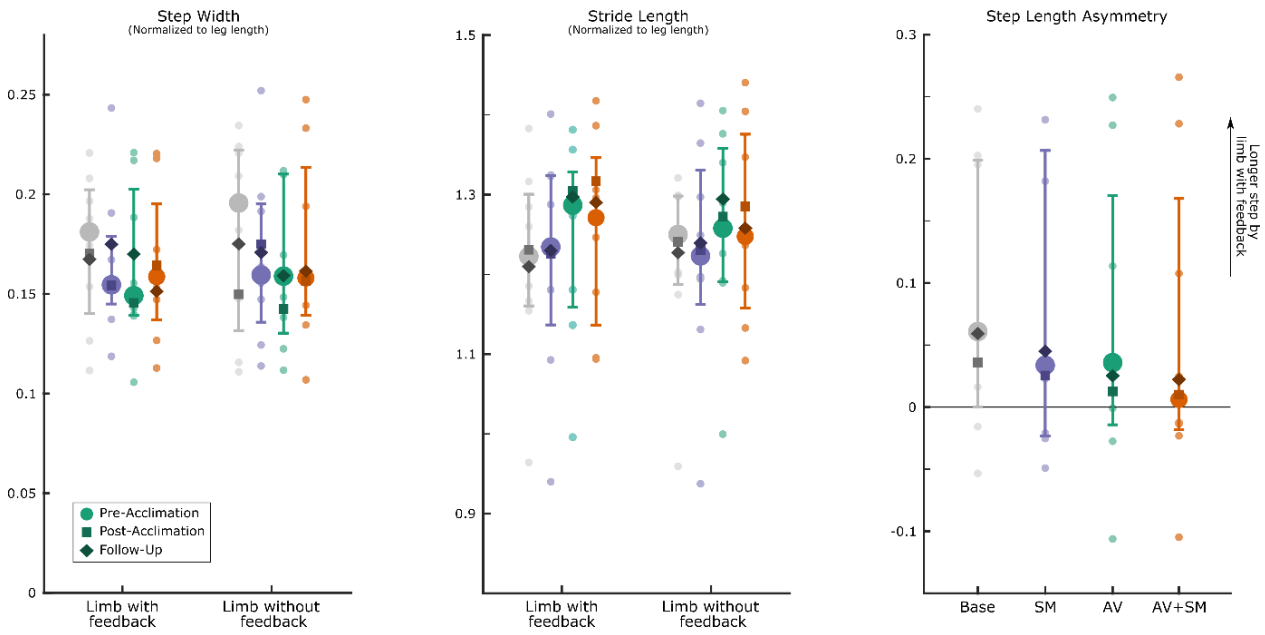

Figure 5.5 Spatiotemporal parameters during early adaptation (strides 1-30) to sensorimotor (AV + SM), audiovisual (AV), and combined (AV + SM) biofeedback at the pre-acclimation visit. Plots

portray median (IQR) as well as individual participant data. A larger value for step length asymmetry (Equation 2) indicates longer strides were taken on the limb targeted by biofeedback and a score near zero indicates symmetry. Step width and stride length have been normalized to leg length for each participant. Median post-acclimation (square) and follow-up (diamond) values are presented for all parameters. Across parameters, no significant differences were observed between each modality and baseline or between modalities.

Kinematic changes were also observed in the less-affected limb, despite the fact that muscle activity was not significantly altered from baseline. Individuals significantly increase knee flexion at initial contact for all biofeedback modalities ($p < 0.046$ for mid-session; Figure A.2.1). Further, AV and AV + SM yielded simultaneous increases in hip flexion, although neither reached significance ($p > 0.06$). Small, but mainly nonsignificant, increases in hip and knee flexion during swing and ankle plantarflexion at push-off were also observed across all modalities

5.3.2 Post-Acclimation Response

Following acclimation and at the two-week follow-up, participants were able to consistently increase soleus activity in response to biofeedback (Figure 5.7). At the post-acclimation visit, mean soleus activity increased by 7.8% [3.5,15.8], 31.5% [19.8,43.8], 35.5% [24.4,45.0] relative to baseline in early adaptation using SM, AV, and AV + SM biofeedback, respectively ($p = 0.02$). However, similar to the pre-acclimation visit, response to SM biofeedback was not maintained ($p > 0.11$ for mid and late phases) and by the follow-up visit, participants demonstrated no response to the SM-only system across all phases ($p > 0.25$). Response to AV and AV + SM biofeedback for both visits was also almost immediate, as individuals demonstrated significant increases in soleus activity within the first five strides of walking with both modalities ($p < 0.031$). Taken together, this indicates that individuals retained the capacity to respond to both the AV and AV + SM modalities, even after two weeks without using the systems. The timing of soleus activity also demonstrated changes following acclimation (Figure 5.4). In particular, at post-acclimation and follow-up, individuals predominantly modulated soleus activity at push-off using

AV and AV + SM biofeedback whereas in the pre-acclimation visit, soleus activity increased across stance phase. However, while participants were able to increase soleus activity with biofeedback, soleus activity still quickly returned to baseline during washout for both the post-acclimation ($p > 0.68$) and follow-up visits ($p > 0.48$). This suggests that there was no after effect of the in-session changes, indicating limited storage of the adapted gait patterns.

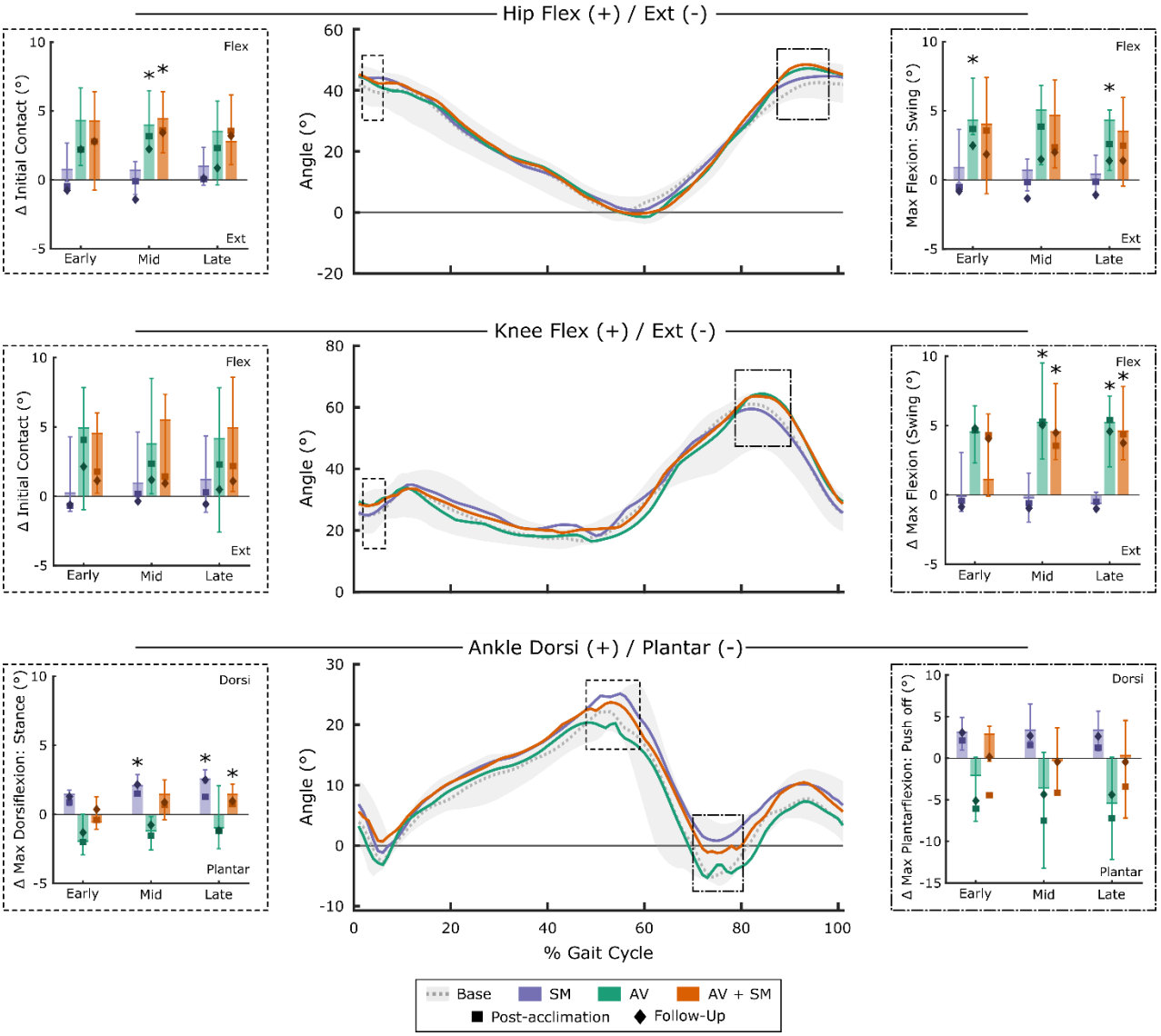

Figure 5.6 Sagittal plane kinematics for the hip, knee, and ankle on the more affected limb during walking with sensorimotor (SM), audiovisual (AV) and AV + SM biofeedback. Middle panels show median trends for all biofeedback modalities and baseline during the late phase (strides 181-210)

*of the pre-acclimation visit. Baseline trends show median (IQR). Bar plots depict median (IQR) changes from baseline for key points within the gait cycle. Initial contact is defined as the mean value over the first 5% of the gait cycle. Median values for post-acclimation (square) and follow-up (diamonds) visits are also presented. Note that because there was inter-participant variability in the timing of maximum angles, there is some discrepancy between the bar plots and median kinematic trends. *denotes significant differences from zero, indicating a change from baseline values ($p < 0.05$; Wilcoxon signed rank tests with Holm-Šídák correction).*

There were notable differences in kinematic strategies across modalities following acclimation (Figure 5.6). In contrast to the pre-acclimation visit, there were no significant differences in hip or knee flexion at initial contact at the post-acclimation or follow-up visits ($p > 0.11$). Further, knee and hip flexion in swing were only significantly elevated from baseline in early adaptation to AV biofeedback ($p < 0.046$ for post-training and follow-up). Participants maintained a similar strategy at the ankle using SM biofeedback before and after acclimation, as they significantly increased dorsiflexion through stance ($p < 0.023$ for all phases in post-acclimation and follow-up). However, in contrast to the pre-acclimation visit, response to the AV and AV + SM systems was similar in both the post-acclimation and follow-up visits (post-hoc pairwise comparison: $p > 0.05$), as individuals walked with greater plantarflexion at push-off using both systems. In the less-affected limb, participants increased knee flexion at initial contact for all modalities ($p > 0.046$) and increased hip flexion in swing using AV + SM biofeedback ($p = 0.046$) during the post-acclimation visit, consistent with the pre-acclimation response. In the follow-up visit, participants also significantly increased plantarflexion at push-off across all modalities ($p < 0.023$).

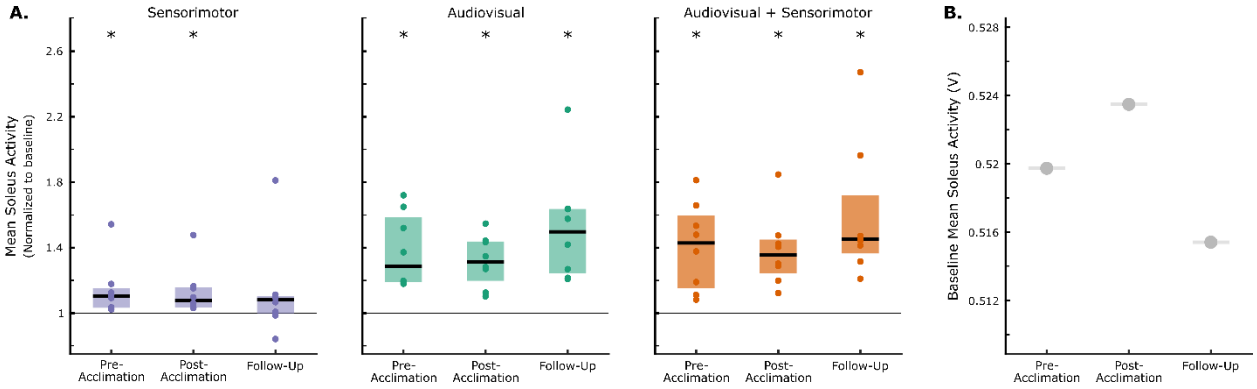

*Figure 5.7 (A.) Mean soleus activity during early adaptation (strides 1-30) to sensorimotor (AV + SM), audiovisual (AV), and combined (AV + SM) biofeedback across the pre-acclimation, post-acclimation, and follow-up visits. For each visit, soleus activity during biofeedback walking was normalized to the first baseline phase performed (B.). * indicates a statistical difference in soleus activity from baseline (Wilcoxon signed-rank tests with Holm-Šídák correction; $p < 0.05$).*

5.4 Discussion

When presented with biofeedback, adolescents with CP were able to rapidly modify soleus activity during walking; however, response varied considerably depending on the modality used to communicate error. Both AV and AV + SM biofeedback elicited consistent increases in soleus activity and gait mechanics within a single session, but individuals adapted gait more quickly to the combined modality. Response to both systems was also consistent immediately following multi-session acclimation and at a two-week follow-up. In contrast, response to SM biofeedback alone unexpectedly decreased within sessions and across subsequent exposures, to the point that it wholly disappeared by the follow-up visit. However, regardless of these differences between modalities, response was entirely contingent on the presence of biofeedback in all cases, as individuals showed minimal retention of the adapted gait patterns once each of the modalities was turned off.

That individuals were able to modulate soleus activity in response to biofeedback indicates that these paradigms may be clinically valuable, even though in-session gains were not retained. Plantarflexor weakness is a common downstream effect of neurologic injury and has been

associated with gross motor function and gait pathology in CP[273,274]. As altered gait patterns impact bony alignment and increase joint pain, which may lead to the eventual degradation of independent walking, improving muscle strength has been a key target in CP rehabilitation programs[7–10]. While traditional weightlifting programs are commonly used to this end, outcomes remain limited as these strategies do not promote strength building within the context of gait[10,275]. Therefore, having an adaptive paradigm that can provide targeted and individualized plantarflexor strength training during walking, may be a valuable addition to rehabilitation.

The noted discrepancy between response to the SM-only system and the other modalities could stem from many sources and provides insight into the mechanisms by which individuals with CP adapt to biofeedback. As both systems presented distinct afferent information, individuals could have been differentially prioritizing AV and SM cues. This aligns with the specificity-of-learning hypothesis which suggests that the sources of error information that are deemed most reliable drive learning whereas all other potential information sources are ignored[134,276]. Because intrinsic feedback pathways (*i.e.*, proprioception, sensation) are commonly affected in CP, it is likely that individuals may automatically weight other sensory information, such as vision, more highly during error correction and perturbation recovery tasks. Prior studies in older adults and individuals with multiple sclerosis lend credence to this hypothesis, as both groups have been shown to be more susceptible to visual perturbation during walking than nondisabled adults, which the authors postulate is likely due to somatosensory deficits[277,278]. Sexton and colleagues made a similar conclusion in nondisabled individuals during reaching tasks, in which they showed that vision is prioritized relative to proprioception when the latter is made artificially unreliable[279].

Differences in response also likely reflected fundamental discrepancies in biofeedback system design. Because the sensorimotor biofeedback system actively made walking more

challenging by resisting the natural motion of the ankle, individuals were more prone to compensating kinematically to bypass the effects of the device. This can be observed in the ankle kinematics, in which participants demonstrated greater dorsiflexion through stance with SM biofeedback compared to the other modalities and baseline walking; similar observations have been reported by Conner and colleagues in response to the SM system used in this study[280]. While participants were instructed to resist the device throughout the walking bout, without the continual prompting afforded by the AV system, they likely prioritized gait strategies which reduced overall effort. This highlights an inherent limitation of resistive SM biofeedback paradigms in isolation and points to the benefit of using parallel AV prompting to continuously focus attention and reinforce desired device engagement.

While the overall magnitude of response to the AV and AV + SM systems were similar, we did note small but significant differences in the rate at which individuals responded to both systems. In line with our original hypothesis, individuals walking with AV + SM biofeedback modified their soleus activity almost immediately whereas adaptation occurred more slowly when the systems were used independently. This suggests that AV + SM biofeedback may have enhanced error recognition and subsequently prompted more rapid movement correction. Prior studies comparing audio and visual biofeedback during gait have reported similar findings, as they demonstrated that nondisabled individuals and stroke survivors alter gait to a greater extent when information is applied multimodally[147,149]. Further, Yen and colleagues demonstrated that a combination of visual biofeedback and resistance, designed to augment proprioceptive information, elicited greater and longer lasting changes in stride length in individuals with incomplete spinal cord injury than either system independently[139]. Counter to these studies, the apparent advantage of the AV + SM biofeedback system used in this study was not maintained

past the beginning of the trial; however, this is likely the result of the rapid attenuation of response to the SM modality, as previously discussed.

Individuals also employed distinct kinematic strategies to elicit change in soleus activity with AV and AV + SM biofeedback. In particular, during the pre-acclimation visit we noted that individuals walking with the AV-only system exhibited greater plantarflexion through push-off than either of the other modalities. Although improving range of motion is generally a target in CP rehabilitation[254], this strategy may have contributed to the proximal compensatory strategies observed during AV walking; increased plantarflexion in early swing may have required individuals to increase hip and knee flexion to create sufficient toe clearance. This highlights a shortcoming of the AV biofeedback system, as it may provide insufficient information to communicate the desired timing and magnitude of gait changes[134]. In contrast, the sensorimotor system only applied resistance during the stance phase, which may have provided more specific cues on appropriate soleus activation timing, decreasing the need for compensation at the hip.

Acclimation to both biofeedback systems also affected how individuals responded to each modality. By the post-acclimation visit, participants increased soleus activity almost immediately after the systems were turned on and the changes were predominantly constrained to push off, suggesting that they had learned how to effectively engage with both systems. This observation aligns with previous studies on motor adaptation which have demonstrated that individuals respond more quickly following repeated exposure of a perturbation, indicating that the central nervous system has stored knowledge of the novel environment[152,186]. During walking with the AV + SM system, participants also significantly increased plantarflexion from baseline at push-off, indicating that they became more adept at overcoming the resistive torque imparted by the SM system. Decreased knee and hip flexion through the gait cycle also indicated that participants were

modulating soleus activity via localized changes at the ankle rather than adopting full-limb compensatory strategies.

Despite the improvements observed following acclimation, individuals did not demonstrate retention of the adapted gait patterns once biofeedback was turned off. Given the length of each walking bout and the number of sessions evaluated in this study, we did not anticipate that there would be significant transfer of in-session gains. However, because participants did not significantly decrease response to biofeedback, even after a two-week washout, this suggests that with extended training, there may be larger carry over effects. Prior work by Conner and colleagues previously demonstrated that individuals with CP had measurable improvements in soleus recruitment, co-contraction, and energy expenditure during overground walking following a 10-12 session training program using SM biofeedback independently[27,40,281]. Because we saw that AV biofeedback further amplified response, we anticipate that training outcomes could be even greater with AV + SM training. Transfer may have also been affected by the manner in which biofeedback was administered within each session. Prior evidence has suggested that both the timing and the frequency with which cues are presented may influence retention of adapted gait patterns. We elected to provide all biofeedback concurrently during walking, as evidence suggests that continual reinforcement of the desired trajectory is critical in the early stages of learning a complex motor task[134]. However, participants likely developed dependence on the biofeedback system to prompt gait changes. Employing fading or intermittent biofeedback paradigms, in which progressively less guidance is provided with skill acquisition, may force participants to rely more heavily on their own error estimation and correction pathways which, in turn, may promote longer-term transfer[134,282–284]. Understanding the factors that influence if and how gait modifications are retained

outside of the context of biofeedback training will be a critical area for future research if it is to be considered a viable rehabilitation strategy for individuals with CP.

Finally, across visits and biofeedback modalities, we noted a high level of inter-participant variability in response. This suggests that beyond the choice of modality, there are many other participant and system-level factors that may affect how an individual interacts with biofeedback. Because we were using a multimodal paradigm, which included a resistive ankle exoskeleton, individuals' selective motor control about the ankle, muscle strength, and proprioception may have all influenced outcomes. Prior work has also indicated that an individual's capacity to modify feedforward gait strategies in response to perturbation and temporarily store the adapted pattern is contingent on both the severity and location of the primary neurologic injury[159]. Other participant-level factors such as individuals' age and dual-task capacity may have further influenced their comprehension of the biofeedback systems and their motivation to modify gait accordingly. Response following the acclimation visit may have also differed if acclimation protocols had been individualized; for this application all individuals underwent the same four acclimation sessions with AV + SM biofeedback which was likely insufficiently challenging for some individuals and overtaxing for others[271]. Given this complexity, there is a need to develop robust analytical techniques to comprehensively model these participant-device interactions. To this end, prior studies have explored using causal modeling to identify factors which contribute to gait mechanics following surgical intervention and elevated energy costs in CP[285–287]. Applying a similar strategy to understand biofeedback outcomes may inform how systems can be designed to optimize responses and aid in selecting candidates for training.

To our knowledge, this is the first study to compare how the choice of biofeedback modality may influence response in CP; however, there are limitations to our approach that need

to be considered. We evaluated a small and highly heterogeneous sample of individuals. While this allowed us to demonstrate that biofeedback may be beneficial for a broad user base, it did limit our statistical power. We also did not compare response to the audio or visual systems independently. This was motivated by the fact that we were primarily interested in contrasting the effects of intrinsic versus extrinsic biofeedback systems rather than provide a comprehensive understanding of response to many distinct forms of extrinsic feedback. But, as audio biofeedback may be particularly advantageous for administering training during overground walking, characterizing how response may change if visual information is also omitted is an important area for future research. We fixed speed across sessions to control for any potential confounding effects that changes in speed may have on kinematics and muscle activity. However, this may have inadvertently introduced a ceiling effect on the extent to which individuals could effectively modulate soleus activity. We were also unable to directly compare the magnitude of response across the three visits due to the manner in which we normalized EMG data. We elected to normalize all activity to the first baseline phase tested within each visit, rather than a maximum voluntary isometric contraction (MVIC), given the challenges of collecting reliable MVICs in children with neuromuscular disorders[288]. As such, there were differences in the baseline activity used for normalization which limited inter-session comparison (Figure 5.7). Interestingly, baseline activity appeared to increase at post-acclimation, which suggests that individuals were able to modulate soleus activity to a greater extent following the acclimation sessions; however, additional work is needed with a reliable normalization strategy to confirm this observation. Finally, as previously described, this study was not designed to specifically evaluate training outcomes due to time and resource constraints. As the goal of biofeedback training is to ultimately improve

functional outcomes in CP, evaluating how response to each biofeedback modality changes across a longer training protocol is a critical next step of this work.

5.5 Conclusion

Evaluating multi-session response to AV and SM biofeedback systems demonstrated how individuals with CP differentially prioritize distinct modes of biofeedback. This analysis revealed that individuals are capable of modulating muscle activity in response to biofeedback, but both the rate and magnitude of adaptation is sensitive to the modality used. Specifically, we found that AV biofeedback consistently amplified participant responses whereas responses to SM biofeedback were more transient. Secondarily, we observed that individuals became more adept at responding to biofeedback with repeated exposure. Evaluating how the choice of biofeedback modality affects response is a necessary first step in informing future system design such that biofeedback gait training can become an efficacious clinical strategy to improve mobility in CP.

Chapter 6

MULTI-SESSION ADAPTATION TO AUDIOVISUAL AND SENSORIMOTOR BIOFEEDBACK IN CEREBRAL PALSY

In preparation

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ABSTRACT

Background: There has been growing interest in the use of biofeedback to augment gait training in cerebral palsy (CP). To this end, audiovisual, sensorimotor, and immersive biofeedback paradigms have been used to elicit short-term gait improvements; however, outcomes remain persistently variable. Because biofeedback training requires that individuals can adapt their gait pattern in response to feedback and retain these changes across sessions, deficits in either capacity may affect outcomes. Yet, neither has been explored extensively in CP.

Methods: In this study, we evaluated the extent to which adolescents with CP (7M/1F; 14 years [12.5,15.26]) could adapt gait and retain improvements across four, 20-minute acclimation sessions with audiovisual and sensorimotor biofeedback. The objective during these sessions was to increase plantarflexor activity, with audiovisual biofeedback indicating soleus muscle activity and sensorimotor biofeedback provided by a bilateral resistive ankle exoskeleton. We quantified the time-course of change in muscle activity within and across sessions as well as overground walking function before and after the four sessions.

Results: All individuals were able to significantly increase soleus activity from baseline using biofeedback ($p < 0.031$) but demonstrated different adaptation strategies across sessions. For example, the majority of individuals demonstrated the greatest increase in soleus activity in Session 3 whereas others had a consistent response across all sessions. The magnitude of in-session soleus modulation also had a moderate positive correlation with retention of the adapted gait patterns, suggesting that adaptation capacity may be a determinant of responses. However, despite these improvements in soleus recruitment, gait mechanics, speed, and motor control complexity during overground walking was not significantly altered after the four acclimation sessions ($p > 0.15$).

Conclusions: This work suggests that individuals with CP have the capacity to adapt their gait pattern using biofeedback, but responses are highly individualized. Characterizing adaptation to biofeedback systems may be promising avenue with which to understand the variability of existing outcomes in biofeedback training and inform the design of systems that can be optimized for each individual and integrated into clinical care.

6.1 INTRODUCTION

Among individuals with cerebral palsy (CP), over 70% walk independently or with a mobility aid[52], yet walking is often difficult and may degrade over time, due to a cascade of progressive musculoskeletal impairments (*e.g.*, muscle weakness, contracture, and bony deformity)[5,6]. Because mobility promotes independence in activities of daily living[1–4] and may slow the progression of musculoskeletal impairments[4,7,65,66], gait has become a key target in CP rehabilitation. A variety of intervention strategies have been developed to this end, including strength training, pharmaceutical prescriptions, and orthopedic and neurosurgeries[10]. However, there has been growing interest within rehabilitation in using biofeedback-driven gait training, as it facilitates task-specific and self-initiated walking practice, both of which may be critical for promoting neuroplastic changes[4,22–26,49].

Biofeedback systems are commonly designed to provide audio, visual, or sensorimotor (*i.e.*, tactile or proprioceptive) cues on movement error during walking to reinforce desired gait patterns[134]. In CP, both audiovisual and sensorimotor systems have been used to elicit changes in gait speed[29,31–33], joint kinematics[21,28,29], muscle activity[29,144,289], and, more recently, motor control [27,39,257,265,290]. Although these studies point to the potential efficacy of biofeedback training, outcomes remain variable. For example, Booth et al. recently demonstrated that over 30% of the individuals they evaluated were not able to significantly modify ankle power, knee extension, or step length to reach established targets during visual biofeedback training[34]. Similarly, Levin et al. cited high interparticipant variability in speed, cost of transport, and functional gait outcomes following multi-session training with visual and proprioceptive biofeedback[33]. As such, before biofeedback can be a viable non-invasive rehabilitation strategy, there is a need to better understand this heterogeneity in training responses.

Eliciting positive outcomes to biofeedback requires that individuals are able to both adapt gait and retain in-session improvements, suggesting that deficits in either ability following neurologic injury may adversely affect response. Adaptation capacity during walking is commonly evaluated by systematically introducing a perturbation and measuring the time-course changes in gait. Such perturbations have previously included adding weight to a leg or using a split-belt treadmill to drive both legs at different speeds[159,162,163]. These studies have observed that adaptation is commonly characterized by: (1) a gradual change in gait from baseline, as the central nervous system modifies its feed-forward strategy through trial-and-error in response to the novel perturbation and (2) a brief persistence of the adapted gait pattern once the perturbation is removed, often called an aftereffect[164]. Further, studies have noted that adaptation occurs more quickly with repeated practice, which is used to suggest that the central nervous system has partially retained the novel gait strategy to better accommodate the perturbation[186]. As each of these processes involve supraspinal motor centers, adaptation capacity is often affected among those with neuromuscular disorders and may even vary within subpopulations depending on the size and location of the primary injury[159]. For example, comparative studies in CP[161,162] and stroke[153,174,181–183] have demonstrated that cerebral injury slows the rate at which individuals adapt to perturbation but does not significantly alter the presence of aftereffects. Further, Mawase et al. recently demonstrated that individuals with CP demonstrate faster adaptation across multiple sessions of split-belt treadmill walking, indicating that the CNS can still retain knowledge of novel perturbation environments[186].

Characterizing how individuals adapt gait in response to biofeedback may be critical to understanding the variability of outcomes. However, while these foundational studies in motor adaptation provide a valuable framework to understand adaptation capacity in CP, there is no

evidence to suggest that the findings extend to rehabilitation strategies. In fact, prior work has suggested that because adaptation is driven by error recognition, the extent to which individuals adapt their gait is likely contingent on both the type of perturbation and the manner in which it is applied[162,188]. As such, to understand outcome variability there is a need to directly evaluate adaptation to biofeedback.

The aim of this study was to evaluate the extent to which individuals with CP adapt gait and retain improvements during multi-session acclimation to a multimodal biofeedback paradigm, designed to promote plantarflexor recruitment. Secondarily, we compared overground walking performance before and after acclimation to understand if improvements during biofeedback walking were retained. We hypothesized that, similar to traditional adaptation studies, individuals would modulate plantarflexor activity in response to biofeedback and demonstrate aftereffects immediately following multi-session acclimation, suggesting that in-session gains were temporarily stored. We further hypothesized that the rate and magnitude of soleus adaptation would increase across sessions, indicating that individuals had retained knowledge of how to effectively engage with the biofeedback environment. Extending established frameworks in motor adaptation to evaluate biofeedback will not only bolster foundational understanding of adaptation capacity in CP but will provide insight into potential mechanisms which may underlie existing responses to biofeedback.

6.2 METHODS

6.2.1 Participants

A convenience sample of eight individuals with spastic cerebral palsy were recruited to evaluate adaptation to multimodal biofeedback (Table 6.1). To be eligible for participation, individuals had to be able to (1) walk for ten consecutive minutes on a treadmill, with handrails as needed, (2)

follow simple verbal instructions and (3) respond to audio and visual cues. Individuals were excluded from the study if they were under ten years of age or had received orthopedic surgery or lower limb botox injections within the past six months unless participation was approved by their primary provider. Prior to data collection, all participants and their caregivers provided written consent and the study protocol was approved by the Institutional Review Board at Northern Arizona University.

Table 6.1 Participant Demographics

	Gender	GMFCS Level[a]	Diagnosis[b]	Age (yrs)	Height (m)	Mass (kg)	More-Affected Limb[c]	Walking Speed (nd)[d]
P1	M	II	SD	18	1.76	62.14	R	0.31
P2	M	II	SD	12	1.45	42.41	L	0.28
P3	F	III	SD	13	1.58	42.18	R	0.22
P4	M	II	SD	15	1.65	60.78	L	0.25
P5	M	II	SD	13	1.50	39.01	R	0.31
P6	M	I	SH	12	1.43	39.46	R	0.32
P7	M	III	SD	15	1.56	68.95	L	0.23
P8	M	I	SH	16	1.65	65.77	R	0.27

[a]Gross Motor Function Classification System; Level determined by licensed physical therapist
[b]Diagnoses include: Spastic diplegia (SD), spastic hemiplegia (SH); Diagnosis reported by participant caregivers
[c]Reported by participants
[d]Nondimensional, calculated according to Hof A.L., 1996

6.2.2 Experimental Protocol

Participants completed a four-day protocol using a multimodal biofeedback system during treadmill walking (Figure 6.1). Each session was structured to include baseline walking (1 minute) immediately followed by biofeedback (2, 10-minute bouts) and washout (1 minute) phases. At the transition from the biofeedback to washout phases, the system was turned off and participants were instructed to walk in whatever pattern felt natural; this was included to capture aftereffects which could indicate that the central nervous system had temporarily retained in-session gait modifications[164]. Between the two bouts in each session, participants were required to take a five-minute seated break to mitigate fatigue effects. Across all sessions, participants walked at a

consistent self-selected speed (median [IQR]: 0.805 m/s [0.72, 0.89]) and held onto treadmill handrails as a safety measure.

Participants also completed two assessment visits, performed before and after the biofeedback acclimation protocol, to measure changes in walking function. During the pre-acclimation session, participants were evaluated by a licensed physical therapist who confirmed their GMFCS level and more-affected limb and measured range of motion and spasticity at the knee (flexion/extension) and ankle (dorsi/plantarflexion); spasticity was evaluated using the ordinal Modified Ashworth Scale (0: no spasticity; 4: rigidity). Participants then completed six overground barefoot walking passes at a self-selected speed. At the post-acclimation session, only the overground walking passes were collected. The entire protocol was performed over a two-week period, with 1-3 days of separation between individual sessions.

6.2.3 Multimodal biofeedback

At each session, participants walked with synchronous audiovisual and sensorimotor biofeedback, both of which were designed to promote plantarflexor activity; the plantarflexors were a suitable target for this study, given their importance in generating propulsive forces during walking[5,263]. Audiovisual biofeedback was administered *unilaterally* on the more affected limb using a custom-built system (See Chapter 5.2.4 for full system details). Briefly, this system is designed to present the user with a real-time measure of soleus activity alongside a target score and play a tone any time that score is reached. Based on user success rate, the target score automatically adjusts, which helps to balance user engagement and task-challenge. Sensorimotor biofeedback was administered *bilaterally*, using an untethered ankle exoskeleton that was developed for use in CP[27,39,281] (Full system details are reported elsewhere[39,266]). This system is designed to impart a *resistive* (*i.e.*, dorsiflexion) moment at the ankle proportional to the biological ankle moment during walking to

encourage greater plantarflexor recruitment. A custom-built Matlab interface wirelessly communicates with the device, allowing the researcher to adjust the magnitude of the applied torque within the session. Across sessions, the nominal torque value was adjusted from 0.1 Nm/kg to 0.2 Nm/kg in increments of 0.025 Nm/kg according to the schedule depicted in Figure 6.1; this schedule was selected based on prior studies that have used the same system[27,281]. Further, during both the baseline and washout phases of each session, the exoskeleton was automatically set to 'zero-torque' mode (*i.e.*, 0 Nm/kg), which functionally turned both ankle assemblies into hinge joints.

It is important to note the discrepancy in how both biofeedback systems were administered. While we were able to easily provide bilateral sensorimotor biofeedback, we elected to apply audiovisual biofeedback unilaterally, as we felt that bilateral audiovisual information may adversely affect user comprehension and subsequent outcomes. Although this introduced the potential for asymmetric gait effects, it also provided the opportunity to compare how response differed between a multimodal (*i.e.*, audiovisual + sensorimotor) and unimodal (sensorimotor) biofeedback system.

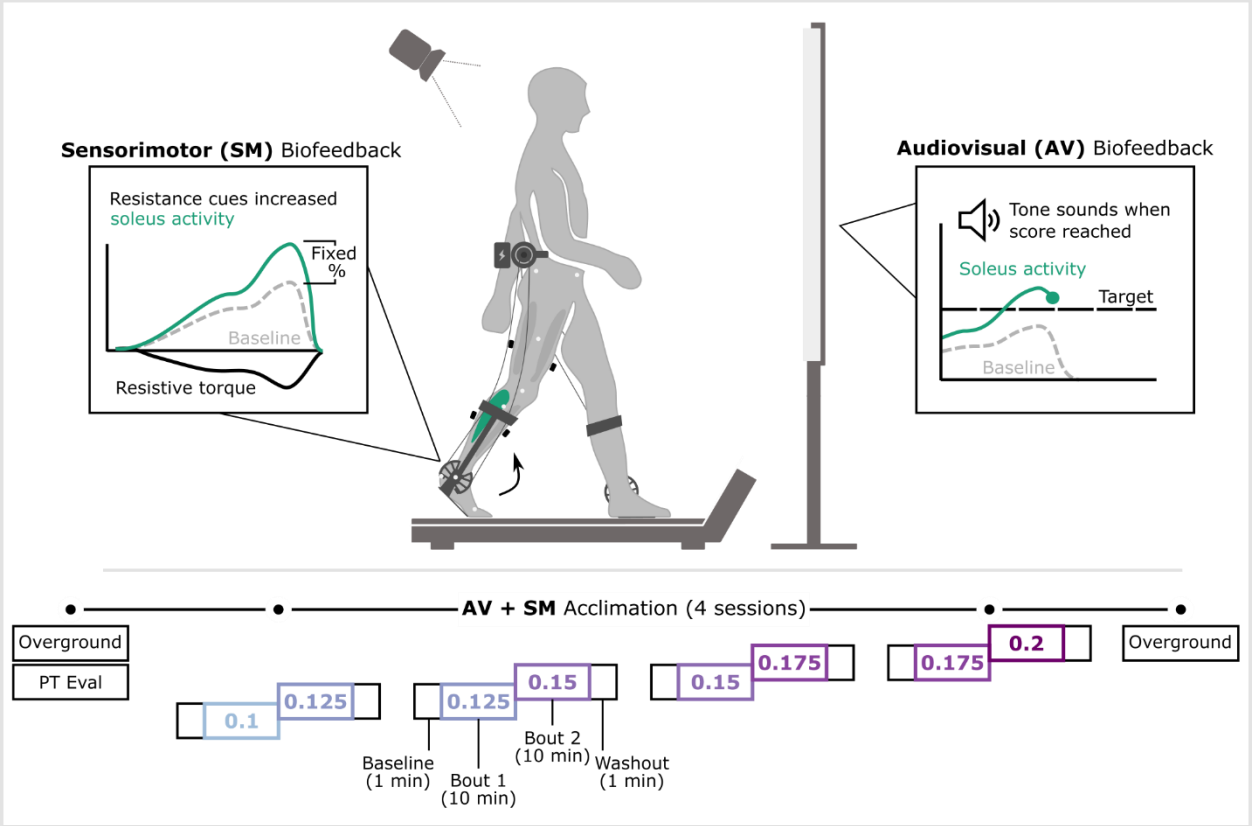

Figure 6.1 Experimental protocol used to evaluate multi-session adaptation to multimodal biofeedback. Participants completed a four-session acclimation protocol using combined audiovisual (AV) and sensorimotor (SM) biofeedback. Audiovisual biofeedback on soleus activity was provided for the more affected limb only whereas sensorimotor biofeedback, administered using a resistive ankle exoskeleton, was applied bilaterally. Each session was separated into baseline (1 min), biofeedback (2x10 minutes), and washout (1 min) phases. The nominal torque value of the ankle exoskeleton was set at 0.1 Nm/kg during the first bout of the first session and incrementally adjusted by 0.025 Nm/kg over the subsequent bouts, as depicted. Overground walking data was collected at pre-acclimation and post-acclimation sessions; a physical therapist evaluation was also performed at the pre-acclimation session. Motion capture data was collected during the pre-acclimation and post-acclimation sessions and electromyography data was collected bilaterally from the vastus lateralis, semitendinosus, soleus, and tibialis anterior across all sessions.

6.2.4 Data Analysis

Bilateral surface electromyography data were recorded for the tibialis anterior (TA), medial gastrocnemius (GAS), vastus lateralis (VL), and semitendinosus (ST) across sessions. For each session, EMG data were low-pass filtered (40 Hz; 4^{th} order Butterworth), rectified, high pass filtered (10 Hz; 4^{th} order Butterworth) and normalized to the 95^{th} percentile of the baseline walking

phase. Additionally, during the pre-acclimation and post-acclimation sessions, synchronous motion capture data were collected using the Vicon Plug-In-Gait marker set (1000 Hz) from which three-dimensional lower limb kinematics (Vicon Plug-In Gait Model) and spatiotemporal parameters (Gait Cycle Parameter Calculator; Vicon ProCalc) were derived. All overground data were subsequently segmented into individual strides using the heel marker to delineate consecutive heel strikes.

6.2.4.1 Multi-session acclimation to biofeedback

During each acclimation session, EMG data were separated into one-minute sections from which both peak muscle activity and motor control complexity were calculated. The latter was defined as the total variance that could be accounted for by a one-synergy solution ($tVAF_1$), derived from non-negative matrix factorization [103]. The formulation is as follows:

$$EMG_{mxt} = W_{mx1} * C_{1xt} + Error \quad (6.1)$$

$$tVAF_1 = \left(1 - \frac{Error^2}{EMG_{mxt}^2}\right) * 100 \quad (6.2)$$

Here, m is the number of muscles (m = 4), t is the number of time points, and W and C represent the synergy weights and their corresponding activation patterns, respectively. The $tVAF_1$ is frequently used as a measure of motor control complexity because it is sensitive to impairment level; individuals with CP and other neuromuscular disorders have higher $tVAF_1$ than nondisabled peers which indicates that their motor control strategy is better-captured by a low-dimensional decomposition and, therefore, less complex[38,41,119,120]. We hypothesized that across successive bouts, we would see a decrease in $tVAF_1$, indicating that individuals were significantly modifying their motor control strategy in response to biofeedback.

6.2.4.2 Pre and Post-Acclimation Analysis

To get a comprehensive understanding of whether in-session improvements using biofeedback were transferred to overground walking, we characterized pre-acclimation and post-acclimation data across multiple functional levels. For all overground strides, the average muscle activity across the gait cycle was computed to quantify if recruitment strategy improved following multi-session acclimation to biofeedback. Further, joint-level changes in gait were evaluated using the gait deviation index (GDI). GDI is a summary measure of kinematics that is used to quantify the extent to which three-dimensional pelvis, hip, knee, and ankle angles align with nondisabled trends[232]. GDI scores are scaled such that a score of 100 indicates the average gait pattern for nondisabled individuals and lower numbers indicate greater levels of gait impairment. For each recorded stride, GDI was computed using a previously published nondisabled data set[232]. Finally, changes in full-body coordination were evaluated using spatiotemporal parameters (*i.e.*, speed, step width, step length, cadence) and motor control complexity ($tVAF_1$). The $tVAF_1$ was quantified using EMG data for seven strides, concatenated across all overground walking passes for each session; the number of strides was held constant for all participants and sessions because $tVAF_1$ is sensitive to the amount of variance in the input data[210]. For any participants that had more than seven recorded strides, strides were randomly sampled without replacement (replicates = 50) to generate a distribution of $tVAF_1$ values from which the mean value was then used.

As a secondary analysis, we compared whether individual differences in baseline walking function, defined by GMFCS level, motor control complexity, and GDI during the first overground visit, correlated to in-session gait adaptation and aftereffects. This was motivated by prior research which suggests that adaptation capacity is related to the extent of neurologic injury and may therefore change according to these common functional measures. We hypothesized that

individuals with better walking function at baseline would have the largest change in gait while using biofeedback and the largest aftereffects.

6.2.5 Statistical Analysis

For all sessions, we evaluated changes in soleus activity and motor control complexity ($tVAF_1$) from baseline at three phases within each bout - early adaptation (first minute), steady-state (minutes 3-8) and late adaptation (last minute) - and the first minute of washout using multiple Wilcoxon signed-rank tests and adjusted for multiple comparisons using a Holm-Šídák correction. To compare response between individual bouts at each phase (*i.e.*, early, steady-state, and late adaptation), we performed multiple Kruskal-Wallis tests; for those tests which reached significance, post-hoc pairwise comparison was performed using Wilcoxon signed-rank tests. Secondarily, a two-way ANOVA was performed on data for each phase to evaluate the effect of bout and session number on soleus activity. Multiple linear regression models were fit to determine if there was a correlation between soleus activity and activity of the other muscles (*i.e.*, TA, ST, VL) within sessions; this was used to understand the extent to which participants were selectively modifying soleus activity in response to biofeedback. Linear regression models were also developed to evaluate if there was a relationship between baseline overground walking function (*i.e.*, $tVAF_1$, GDI, GMFCS) and soleus activity during biofeedback walking and at washout. Finally, overground walking function (*i.e.*, muscle activity, GDI, tVAF1) before and after the acclimation sessions were compared using Wilcoxon-signed rank tests. All analyses were performed using the Matlab statistical toolbox (MathWorks, Natick, USA) and significance was defined as $p < 0.05$.

6.3 RESULTS

Counter to our original hypothesis, the rate at which individuals adapted to biofeedback did not change across sessions. Within the first minute of the biofeedback systems being turned on in each bout, participants increased soleus activity from baseline values ($p = 0.06$; Figure 6.2). However, the initial response to biofeedback was similar between all visits and bouts (Kruskal-Wallis; $p = 0.96$). Interestingly, appeared to be transient during biofeedback walking, as peak soleus activity was consistently lower by the end of each bout, particularly for those during the final two visits; this difference reached significance in the second bout of the third visit (V3-B2), in which peak soleus activity changed from 77.7% [52.9, 128.6] to 51.1% [38.4, 117.8] above baseline between early and late adaptation, respectively ($p = 0.046$). This is a marked deviation from traditional adaptation paradigms and suggests that participants, despite adapting quickly to biofeedback, did not maintain the initial response, likely due to fatigue or engagement. This motivated our decision to define steady-state response as minutes 3-8 of the feedback trail; all remaining analyses are performed using this window.

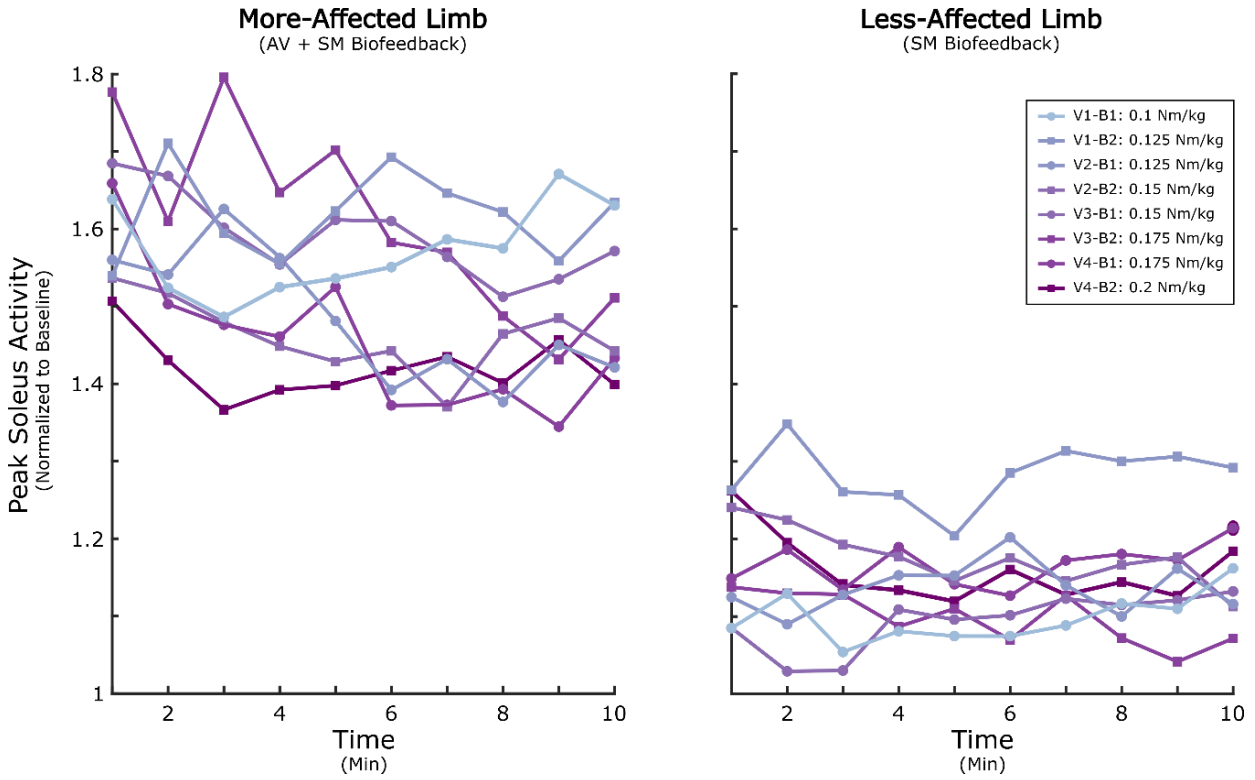

Figure 6.2 In-session soleus adaptation to multimodal biofeedback. Peak soleus activity on the more-affected limb (left) and less-affected limb (right) for each minute of every ten-minute bout. Participants performed two 10-minute bouts (B1-B2) in every visit (V1-V4). For each bout, the resistance level applied by the sensorimotor biofeedback system was incrementally increased from 0.1 to 0.2 Nm/kg (normalized to participant body weight), according to the legend. Soleus activity for each session was normalized to the 95th percentile of the baseline walking phase. Both audiovisual (AV) and sensorimotor (SM) biofeedback were administered on the more-affected limb, whereas only sensorimotor biofeedback was administered on the less-affected limb so as to not impact user comprehension.

At steady-state, participants demonstrated significant increases in peak soleus activity from baseline walking on their more-affected side ($p < 0.031$; Figure 6.3). However, consistent with the observations in adaptation rate, there was no significant effect of bout or visit number on soleus activity and there was no significant interaction between both variables (two-way ANOVA; $p > 0.55$). Despite these group-wise trends, there was a notable amount of variability in responses at the individual level (Figure 6.3); some participants had the greatest steady-state response in Session Three with a sharp decline in Session Four (P3, P5, P6) whereas others (P1, P8, P4) had

generally consistent changes in soleus activity across all sessions, despite the increase in resistance applied by the sensorimotor biofeedback system.

Interestingly, there was no change in steady-state soleus activity from baseline on the less-affected limb across sessions, even though sensorimotor feedback was still being provided ($p > 0.17$). This discrepancy highlights the advantage of augmenting sensorimotor paradigms with audiovisual feedback as a means of focusing attention and enhancing user response (Chapter 5; Figure 6.2)

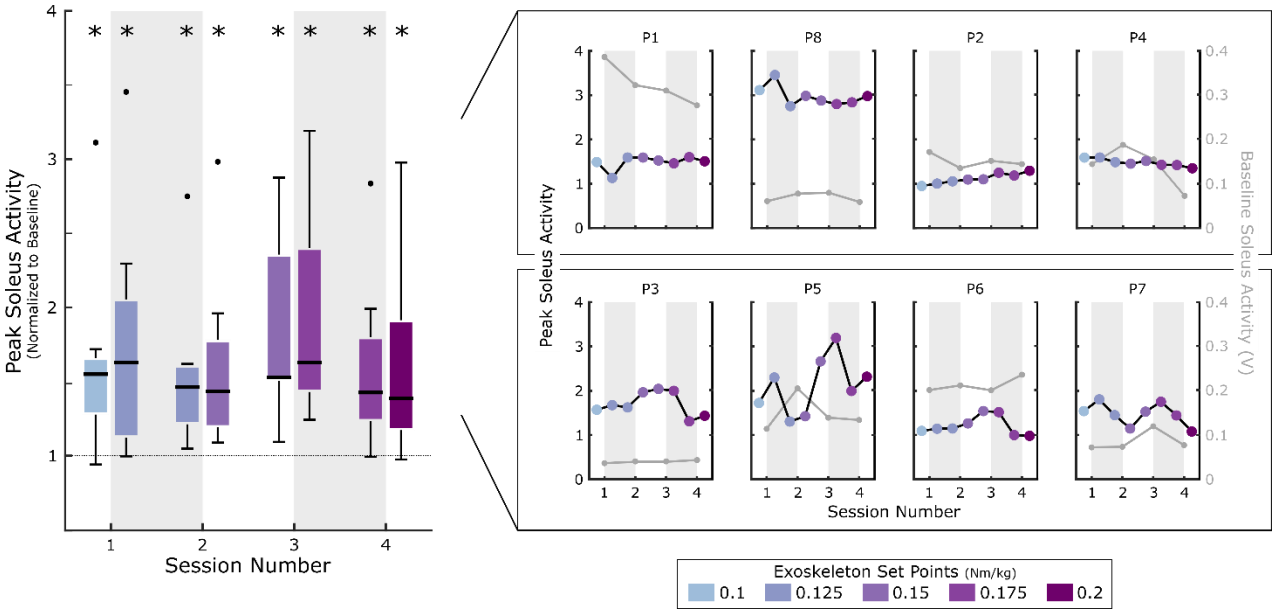

*Figure 6.3 Peak soleus activity across four acclimation sessions with multimodal biofeedback. Peak soleus activity for the more-affected limb across all sessions with combined audiovisual and sensorimotor biofeedback. Each session was separated into two 10-minute bouts of biofeedback walking. Figure data represents activity from minutes 3-8 of each bout, defined as the steady-state response. For each session, data was normalized to the 95th percentile of the one-minute baseline phase. A resistive ankle exoskeleton was used to provide sensorimotor biofeedback and the applied resistance level was incrementally increased from 0.1 Nm/g to 0.2 Nm/kg (normalized to participant mass) across sessions. The left panel depicts group-wise trends, and the right panel shows individual responses as well as baseline soleus activity values (used for normalization). *denotes bouts which were significantly different from baseline walking ($p < 0.05$).*

Once biofeedback was removed, the presence of aftereffects was related to the in-session steady-state response during the second bout (Figure 6.4). For each resistance level, this

relationship generally followed a first-order exponential trend, whereby those individuals that modified soleus activity to a greater extent with biofeedback demonstrated larger aftereffects, up until a certain threshold (~100% of baseline). No relationship was observed between aftereffects and response during the first bout ($R^2 < 0.08$).

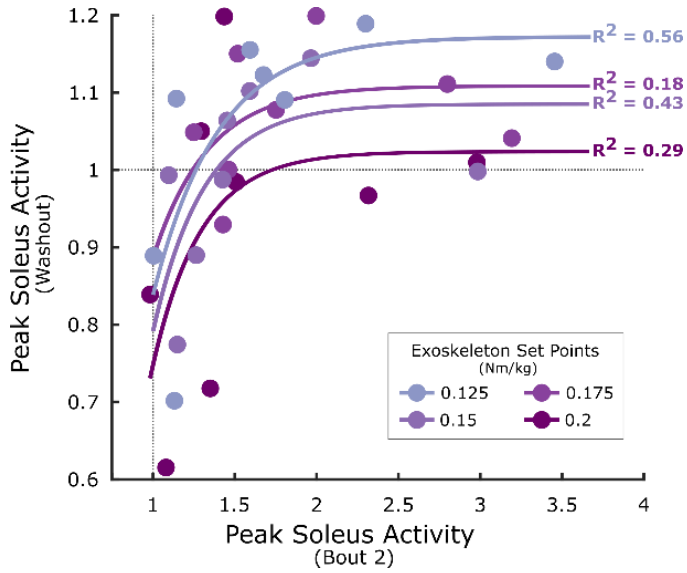

Figure 6.4 Correlation between peak soleus activity during biofeedback and washout phases. Steady-state peak soleus activity in the more-affected limb during the second bout for each session and the washout phase. All data have been normalized to the 95th percentile of baseline activity for each session. A first order exponential model was fit to the data for each resistance level and R-squared values are reported.

In parallel with the changes observed in soleus recruitment during biofeedback walking, there were simultaneous changes in proximal muscle activity. Peak vastus lateralis activity increased from baseline across Sessions 2-4 and semitendinosus activity increased in Sessions 1 and 3, although changes did not reach significance ($p = 0.06$). Further, there was a moderate positive correlation between vastus lateralis and soleus activity that changed as a function of both exoskeleton resistance level and bout (Figure 6.5). In line with the observed changes in muscle activity, motor control complexity ($tVAF_1$) increased from baseline measures across all bouts, reaching significance for the first bout of Sessions 2-3 ($p = 0.03$). This indicates that participants

generally adopted less complex motor control strategies in response to biofeedback, characterized by increased co-contraction of antagonist muscle groups. Note that this analysis was performed on a subset of the population (n = 6), due to EMG sensor loss for P6 and P7.

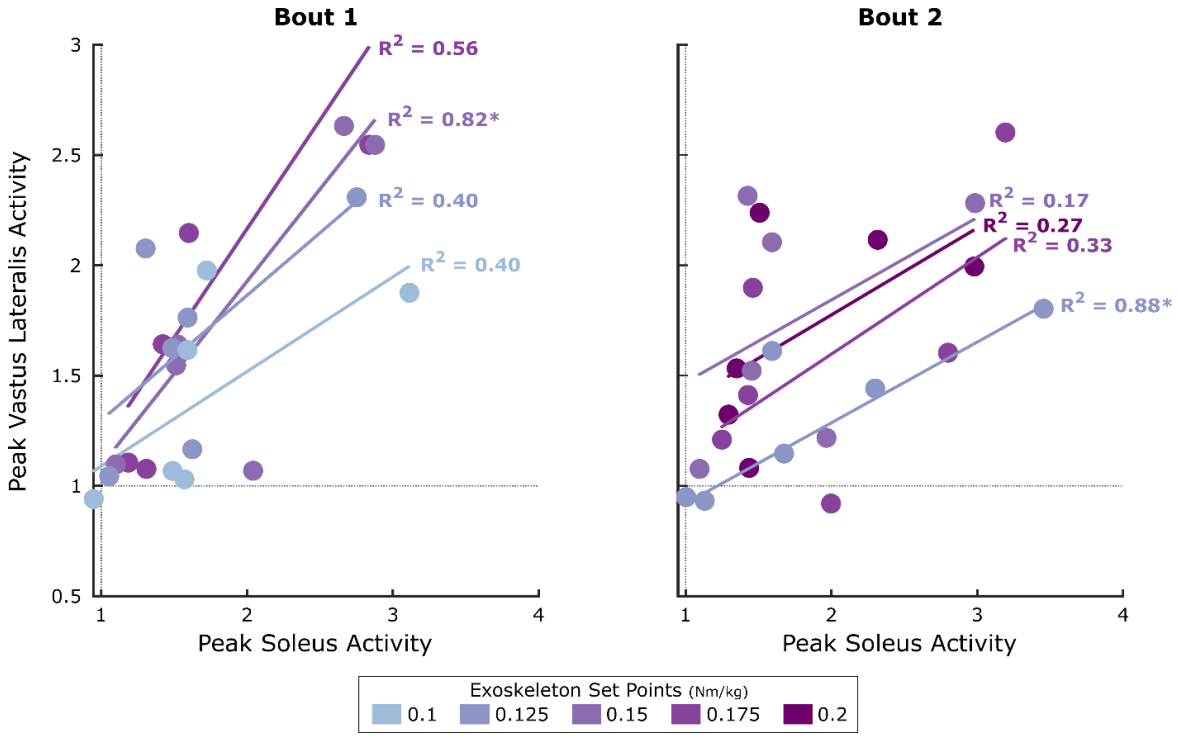

*Figure 6.5 Correlation between peak soleus activity and peak vastus lateralis activity during biofeedback acclimation. Steady-state peak soleus activity in the more-affected limb compared with peak vastus lateralis activity. Data has been normalized to the 95th percentile of baseline walking and separated into the first (left) and second (right) bouts for each session. Colors indicate the magnitude of the resistance being applied bilaterally by the ankle exoskeleton (i.e., sensorimotor biofeedback), normalized to participant body weight. For each resistance level, a linear regression model was fit, and the R-squared values are reported. Note that these trends represent six of the eight participants included in this study, as two had to be removed due to EMG signal loss during acclimation. *indicates that the slopes of the linear models were significantly different from zero ($p < 0.05$)*

Despite the observed in-session changes in soleus recruitment across all bouts, gains were largely context-specific, as there were small but nonsignificant changes in functional measures of overground walking, including mean soleus activity ($p = 0.38$), spatiotemporal parameters (step width, length, speed, cadence; $p > 0.15$), motor control complexity ($p = 0.31$), and GDI ($p = 1$). Further, baseline GDI ($p > 0.08$), $tVAF_1$ ($p > 0.19$), and GMFCS ($p > 0.34$) level were not

significantly correlated with soleus modulation during biofeedback walking or washout across sessions.

6.4 Discussion

Using audiovisual and sensorimotor biofeedback, participants significantly modified soleus activity from baseline measures, however there was not a consistent increase in either the rate or magnitude of soleus modulation across sessions, counter to our original hypothesis. Interestingly, there was a notable correlation between in-session soleus modulation and aftereffects, whereby greater changes in soleus activity during biofeedback walking corresponded to larger aftereffects once the systems were turned off. However, these short-term adaptations were quickly washed out, as individuals did not demonstrate significant changes in muscle recruitment, gait mechanics, or motor control during overground walking following multi-session acclimation to biofeedback. Further clinically relevant measures of walking function were not correlated with in-session improvements in soleus activity or the magnitude of aftereffects.

Although at the group-level, we did not observe consistent changes in soleus recruitment across sessions, there were notable participant-level differences in response. While our correlation analysis indicated that common functional measures (*i.e.*, motor control complexity, gait mechanics, or GMFCS level) were not strongly correlated with in-session adaptation, other participant-level factors, such as fatigue, may have influenced adaptation capacity. Because both biofeedback systems were designed to consistently provide task challenge, the protocol was likely fatiguing for participants. In fact, we observed that soleus modulation was transient within bouts, whereby response was consistently smaller by the end of the session. This was particularly noticeable for the later sessions in which the resistance provided by the SM system was the highest. There was also a positive correlation between proximal muscle activity and soleus activity which

changed as a function of both resistance level and bouts. Taken together, this suggests that as individuals fatigued, they may have been more prone to adopt distinct compensatory strategies (*e.g.*, increased knee flexion through stance) to avoid engaging with the biofeedback systems and thereby reduced the overall soleus engagement. This aligns with prior work by Conner et al. who demonstrated that kinematic compensation was predictive of soleus activity during walking with the SM biofeedback system used in this study and highlights the need to closely monitor both fatigue levels and kinematic compensation during biofeedback walking[280].

Beyond fatigue, differences in sensory integration may have contributed to in-session response. The central nervous system relies on sensory information to detect errors between predicted and actual movement patterns and update its internal models (*i.e.*, sensorimotor calibration) of the environment accordingly. As such, if these afferent pathways are disrupted due to neurologic damage, adaptation may occur more slowly; increases in sensory noise due to greater stride-to-stride variability during gait may have a similar adverse impact on adaptation[186]. This is supported by prior evidence which demonstrates that individuals with cerebral injury due to CP, stroke, traumatic brain injury, or hemispherectomy, adapt more slowly to split-belt treadmill or single-leg weighting perturbations than nondisabled peers[159,161,162,165,184]. Further, Lei Y and Wang recently reported that there is a negative correlation between the variability of proprioceptive signals and visuomotor adaptation rates in older adults during reaching tasks[291]. While the intent of providing augmented audiovisual and sensorimotor biofeedback was to supersede these potentially unreliable sources of afferent information and, therefore, facilitate adaptation, discrepancies in sensory information may still have contributed to the observed heterogeneous response. As such, integrating measures of proprioception into biofeedback studies in CP will provide additional insight into the potential mechanisms underlying adaptation.

We also observed that in-session gains were positively correlated with aftereffects during washout. Prior work has hypothesized that the aftereffects observed once a perturbing environment has been removed provide a measure of the extent to which the central nervous system has temporarily modified its internal model to meet the task demand[152]. Our findings suggest that those individuals with the greatest adaptation capacity demonstrated the largest aftereffects. Interestingly, in line with our observations on in-session adaptation capacity, we found that functional measures of gait (*i.e.*, motor control complexity, GDI, GMFCS) were not significantly correlated with the magnitude of washout for any session ($p > 0.08$). These findings align with prior work in individuals following hemispherectomy and stroke which reported that there was no correlation between aftereffects and degrees of clinical impairment[153,165,292]. While the cerebellum is primarily thought to be involved in adaptive processes, a structure which is commonly preserved in CP, this finding is not entirely unexpected. However, it highlights that beyond standard functional measures, measures of adaptation capacity may be critical to consider in clinical decision making when identifying optimal candidates for biofeedback paradigms.

Beyond differences in adaptation capacity, the structure of the acclimation protocol may have also affected individual responses across sessions and during overground walking. In biofeedback system design there are myriad tunable parameters that may influence response including the modality used to communicate error information, the gait metric targeted, and the frequency and timing of individual cues. In this study, we provided concurrent biofeedback across every session. While this may be advantageous in the early stages of learning a novel task, it can simultaneously foster reliance on extrinsic sources of error information over intrinsic pathways, such that once the system is removed, individuals return to baseline function[134,282–284]. To counter this, prior evidence has demonstrated that providing feedback at the end of a task (often called a

knowledge of results paradigm) or interleaving randomized non-feedback cycles into sessions may strengthen individuals' capacity to independently recognize and correct movement error[22,134]. Administering biofeedback on a treadmill may have also attenuated transfer to overground walking. Not only did it confine individuals to walking at a consistent speed, which may be disadvantageous when attempting to modulate plantarflexor activity, but prior work has demonstrated that adaptation may be highly context dependent. Specifically, the visual-proprioceptive mismatch inherent in treadmill training paradigms has been hypothesized to cause individuals to develop environment-specific internal models, meaning that task learning may improve but may not be generalizable across all walking configurations[189]. Finally, the structure of the acclimation protocol, specifically the number of sessions tested and the time between individual sessions may have influenced both inter-session response and transfer. Prior work by Conner et al. demonstrated that a ten-session protocol was sufficient to elicit changes in both motor control and overground walking function in individuals with CP[281]. Further, Mawase et al. demonstrated that individuals with CP continued to demonstrate improvements in adaptation to split-belt treadmill walking across thirty practice sessions[186]. These studies suggest that we may have provided insufficient practice for individuals to see measurable improvements in walking performance. Variable time between sessions may have had a similar effect. Although all sessions were spaced 1-3 days apart, this timing may have introduced distinct confounders; scheduling sessions too close together may provide insufficient recovery time, and therefore increase the likelihood of rapid fatigue whereas scheduling sessions too far apart may result in prior gains being fully washed out. Together this highlights the inherent complexity of designing effective biofeedback training protocols and the need to develop robust research techniques to systematically characterize how each factor may uniquely contribute to participant response.

While this study marks a critical step in understanding multi-session adaptation to biofeedback in CP, there are some limitations that must be considered in interpreting the results. We reported that the rate of adaptation did not change across sessions by comparing data from the first minute of walking in each bout. This was motivated, in part, by prior studies which have demonstrated that adaptation to split-belt treadmill and single-leg weighting paradigms typically occurs over a 10-15 minute window in nondisabled adults and occurs even more slowly for those with neuromuscular impairments[160,160,167,175,176]. However, it is possible that adaptation may have occurred on a shorter time scale than we were able to measure (Chapter 5). Due to time constraints in our protocol and the limitations of our data collection space, we were unable to measure gait kinematics or kinetic during walking and therefore could not evaluate soleus adaptation on a stride-by-stride basis. This also restricted us from measuring how stride-to-stride variability changed within and across sessions, which may be a critical metric to characterize both learning and fatigue[186]. Together, these limitations highlight a critical next step of this work that will further advance understanding of how adaptation changes as a function of practice. This analysis was also performed in a small population which limited our statistical power. Although the heterogeneity of our population enabled us to capture many different responses to biofeedback and demonstrate the feasibility of using this paradigm for individuals within multiple functional groups, it limits the extent to which our conclusions can be applied to a broader population. Finally, given the difficulty of collecting reliable maximum voluntary isometric contractions for individuals with CP[288], we elected to normalize EMG data to the peak baseline activity for each session. While there was no difference in baseline activity across sessions at the group level (Kruskal-Wallis; $p > 0.88$), thereby justifying our decision to make inter-session comparisons, some participants did demonstrate large deviations in baseline activity which could have influenced the trends shown in

Figure 6.3. This highlights an inherent limitation of evaluating EMG data across multi-session protocols, as effective normalization parameters are challenging to establish, particularly among those with neuromuscular disorders.

6.5 Conclusion

This study demonstrated that individuals with CP can consistently modify gait in response to combined audiovisual and sensorimotor biofeedback, but do not demonstrate consistent inter-session improvements in adaptation. However, it also revealed a high level of inter-participant variability adaptation capacity and aftereffects. As such, understanding the system and participant-level factors which influence response to biofeedback is a critical area for future research. Not only will this aid in the intentional design of biofeedback systems and training protocols but it will help to identify individuals that may benefit from training, ultimately improving the efficacy of biofeedback as a clinical rehabilitation strategy.

Chapter 7

CONCLUSION AND FUTURE WORK

7.1 SUMMARY

The goal of this dissertation was to systematically understand the efficacy of using biofeedback to target and improve motor control in CP. Drawing from multidisciplinary experimental frameworks, we performed a series of studies to characterize the extent to which individuals can selectively modulate motor control in response to biofeedback and how this capacity may be influenced by neurologic injury and biofeedback system design**.** As such, this dissertation makes significant contributions toward understanding the neural control of movement and hastening the development of individualized rehabilitation strategies.

The first objective of this dissertation was to evaluate the extent to which common CP gait patterns affect motor control in order to improve understanding of the factors which may contribute to simplified motor control observed in CP (Chapter 3). We demonstrated that motor control was not significantly altered when nondisabled individuals emulated crouch gait and equinus (*i.e.*, toe-walking) and was significantly different from motor control in a matched CP cohort. This suggests that the simplified motor control in CP is not solely the result of the biomechanical constraints imposed by pathologic gait patterns and is, therefore, largely neurogenic. This study provides important insight into why motor control parameters are often unaffected following interventions designed to improve pathologic gait. Secondarily, the results underscore the value of integrating measures of motor control into clinical care as a means of capturing salient features of the primary injury.

Building off of the findings from the first objective, we then used motor control-based biofeedback to evaluate whether motor control was equally robust across a much broader array of

achievable gait patterns (Chapter 4). Secondarily, we used non-parametric machine learning techniques to model the relationship between gait changes and motor control complexity to inform the selection of biofeedback metrics capable of improving motor control. This work demonstrated that nondisabled adults can dynamically simplify motor control during walking, but the extent to which motor control is changed is contingent on both the magnitude and type of imposed biomechanical constraints. Specifically, the outcomes from our model demonstrated that motor control was most sensitive to changes at the ankle and knee. This was the first study to evaluate motor control over such a diverse range of gait patterns and the first to deploy a motor control-based biofeedback system to evaluate the neural control of gait.

For our final two objectives, we extended our work into CP, to evaluate the capacity for individuals to improve motor control during walking and how the choice of both biofeedback modality and training affected response. In Chapter 5, we deployed two biofeedback systems - designed to provide sensorimotor and audiovisual feedback to encourage plantarflexor engagement - to evaluate how both the magnitude and rate of gait adaptation changed as a function of the biofeedback modality used. We demonstrated that individuals with CP largely rely on audiovisual cues in guiding movement correction but that pairing both modalities to offer simultaneous extrinsic and intrinsic error feedback may promote more rapid gait adaptation. Further, in Chapter 6 we evaluated response to both biofeedback modalities across multiple sessions to understand whether individuals adapted gait more quickly and to a greater extent with practice, which may suggest that they had partially retained the adapted gait pattern. We did not observe consistent improvements in either the rate or magnitude of gait adaptation across sessions and participants; rather, we noted a high level of inter-participant variability in response. However, in-session adaptation capacity was positively correlated with short-term retention of the adapted

gait patterns whereas other standard measures of walking function (*i.e.,* motor control complexity, GMFCS) were not. This suggests that training responses to biofeedback are highly individualized, warranting future investigation into the other factors which may underlie response. Further, results from this study highlight that measures of adaptation capacity encode information about how an individual may respond to multi-session biofeedback training that is not currently captured by more traditional clinical measures of walking function.

7.2 Future Work

The work outlined in this dissertation lays the foundation to understand heterogeneous responses to biofeedback which will advance biofeedback as a clinically viable intervention in CP. It also highlights exciting avenues for future research in biofeedback system design, motor control, and motor learning which will improve scientific understanding of neurologic injury and further expedite the development of intentionally designed tools for gait rehabilitation. The following section outlines some of those avenues in order to inspire future scientific inquiry:

Advancing understanding of the plasticity of motor control patterns

Characterizing the relative robustness of muscle synergies following neurologic injury will inform optimal windows for intervention.

- ***How does motor control change with development for individuals with CP?***

  A critical open question within CP rehabilitation regards identifying the optimal time to intervene. It is generally understood that early intervention (*i.e.*, before 2 years) is likely to elicit the greatest improvements in motor control and gait function, as that is the period over which the central nervous system is the most plastic[87,293]. However, there is still limited understanding of how motor control strategies develop following neurologic injury and, therefore, how wide this intervention window may be. Capitalizing on muscle synergy

analysis techniques, used throughout this dissertation, we can start to quantify when and how motor control strategies following neurologic injury diverge from strategies observed in nondisabled individuals. This will not only provide greater insight into how the central nervous system matures to produce coordinated movement but will inform the design of novel and age-appropriate intervention strategies that can take advantage of these periods of heightened neuroplasticity.

- ***To what extent can motor control be flexibly modified following neurologic injury?***

  Beyond characterizing how synergies change with development, there is also a critical need to understand the capacity for individuals with CP to flexibly modify synergy recruitment. Existing studies of synergies in CP have been primarily focused on comparing synergies to nondisabled peers and evaluating synergies before and after treatment[35,38,44]; there has been minimal work in this population investigating how synergy recruitment may change as a function of task demand. In Chapter 4, we demonstrated that nondisabled individuals can broadly modulate motor control complexity during walking, but hypothesized that this flexibility may directly reflect greater supraspinal involvement in the control of movement and, therefore, be more limited in CP; this finding aligned with and contributed to an extensive body of literature evaluating synergy recruitment across distinct biomechanical contexts[106,110–112]. By extending the experimental and analytical framework developed in Chapter 4 to individuals with CP, we can start to probe if the capacity to alter synergy recruitment during walking is retained following neurologic injury and, importantly, what factors may be associated with any observed changes. Outcomes from this work would further aid in the selection of metrics that can be targeted via biofeedback training to improve motor control.

Untangling heterogeneous response to biofeedback training

Biofeedback has the potential to advance clinical care in CP, but myriad factors may influence whether an individual has a positive training outcome.

- ***Can we leverage causal modeling techniques to understand and predict responses to biofeedback training?***

  As discussed in Chapter 5 and Chapter 6, there is a high level of inter-participant variability in response to biofeedback training. While we demonstrated that both the modality of biofeedback used and an individual's adaptation capacity may partially underlie response, many other factors may dictate if and how an individual responds to biofeedback training. These include an individual's proprioception, dual-task capacity, fatigue levels, and age, as well as whether they adopt undesirable compensatory strategies during training. They may also include elements of the biofeedback training design such as the challenge progression within and between sessions, the time between training sessions, the length of individual training sessions, the gait parameter targeted, and the frequency and timing of biofeedback.

  To understand the complex and multifactorial response to biofeedback training and begin identifying parameters that may be predictive of positive outcomes, we can leverage techniques from the field of causal inference. While recent work by Schwartz et al.[285] provides a detailed overview of causal inference within the context of biomechanics research, briefly, it is a technique that can be used to systematically model relationships between individual predictor variables (*e.g.*, training length, functional ability) in order to define an input set for a machine learning model, such as BART (used in Chapter 4). This technique has been recently implemented in CP to identify the causal effects that contribute

to gait mechanics following surgery[287] and elevated energy costs[286] during walking. Taking a similar analytical approach in the context of biofeedback training would allow us to identify the causal effects of participant and system parameters on training response. This would both inform future biofeedback system design and aid in the identification of candidates for biofeedback training.

- ***How might multisensory cues be differentially prioritized during biofeedback training among individuals with neuromuscular injury?***

  In Chapter 5 we observed that combining sensorimotor and audiovisual biofeedback, while potentially modifying the rate of adaptation, did not appear to have an additive advantage over the audiovisual system alone. While many factors could underlie this response, as discussed, it could suggest that individuals were differentially prioritizing distinct afferent cues. This aligns with the specificity-of-learning hypothesis which states that the most optimal sources of afferent information for a given task drives learning while other potential sources of information are ignored[134,276]. As such, to better understand response to both modalities of biofeedback, there is a fundamental need to understand how individuals with CP may differentially weight or prioritize incoming sources of afferent information. Prior studies in both individuals with multiple sclerosis[277] and nondisabled adults[294] have evaluated this question using a combination of mechanical and optical flow paradigms to systematically introduce perturbations of varying magnitude and direction. Measuring response to both types of perturbation can then be used to understand the weight assigned to each cue. Extending similar paradigms into CP would enable evaluation of how each source of information shapes motor response and may inform multimodal biofeedback design.

Translating biofeedback training into clinical care

Existing biofeedback systems have been primarily evaluated in lab-based environments, raising questions as to their validity in clinical care.

- ***How does multimodal biofeedback training compare to standards of care within rehabilitation?***

  While prior work in CP has indicated that biofeedback training is a promising non-invasive strategy to integrate into CP care, the current strength of evidence is generally low due to inconsistent study design, small sample size, and lack of sufficient control groups[22]. As such, there is a fundamental need to develop large-scale prospective studies comparing the effect of biofeedback gait training to more traditional therapeutic interventions in CP. Evaluating the multimodal platform used in this dissertation (sensorimotor + audiovisual) over a timescale longer than was feasible for the pilot studies described in Chapter 5 and Chapter 6 will provide greater insight into the amount of training required to elicit transferable gait improvement and inform appropriate therapy dosing. It will also enable us to examine how different biofeedback administration strategies (*e.g.*, fading or intermittent feedback) affect the rate of learning. Outcomes from this work would fill a critical gap in biofeedback research which is currently inhibiting larger-scale translation into clinical care.

- ***Can motor adaptation capacity be used to identify candidates for biofeedback training?***

  In Chapter 6, we demonstrated that adaptation capacity, defined here as the ability to modify gait in response to perturbation, was positively correlated with short-term retention of adapted gait patterns and may, therefore, be a key predictor of an individual's ability to respond favorably to long-term biofeedback training. As such, there may be clinical value

in developing standardized methods of quantifying adaptation capacity to inform treatment planning. Traditional analytical techniques in motor adaptation (*i.e.*, split belt or weighted leg paradigms) may be useful to this end, as they require minimal time and equipment to perform. However, it is currently unknown whether adaptation capacity, as measured through these standard techniques, correlates with adaptation to biofeedback. Beyond identifying a measure that may be clinically valuable to integrate into standard patient assessments, outcomes from this work would also add to the limited literature base on motor adaptation in CP (see Section 2.4).

- ***How might biofeedback systems be designed to improve skill transfer?***

  As demonstrated in Chapter 5 and Chapter 6, in-session response to biofeedback may not be retained outside of the training environment. Many of the tunable parameters in biofeedback training may affect transfer including both the length of training sessions and the number of sessions a person undergoes, making it necessary to model the causal effects of each, as described above. However, it is also hypothesized that retention of adapted gait patterns is highly dependent on the context in which the individual initially adapts. This is supported by prior work which has demonstrated that the lack of optic flow provided during treadmill walking can adversely impact transfer of an adapted gait pattern to overground walking scenarios[189]. As such, there is a need to understand how context influences adaptation in CP and develop strategies that emulate natural learning environments to improve skill transfer. Not only can wearable sensors be leveraged to this end (discussed below), but immersive feedback environments (*i.e.,* virtual and augmented reality) may offer the opportunity to enhance transfer while maintaining the high repetition training afforded by treadmill paradigms.

- ***How can wearable sensing be leveraged to extend biofeedback training outside of traditional clinical environments?***

  For biofeedback training to be broadly available and facilitate greater transfer of in-session gains to daily life, it needs to be extended outside of traditional clinical spaces. With the ubiquity of low-cost wearable sensors, it has become even more possible to develop flexible platforms that can be used in home and community-based environments. An advantage of the sensorimotor system used in this dissertation is that it is untethered and, just recently, app-controlled meaning that it can be easily extended into home training programs; however, this paradigm still might be inaccessible to many families due to cost. Developing sensorimotor and audiovisual platforms that capitalize on low-cost sensing will improve the accessibility of biofeedback training. Further, comparing home-based and clinic-based training programs will highlight potential challenges of the latter (*i.e.*, participant compliance, sufficient coaching, etc.) and inform system redesign in order to promote effective use in these environments.

The overarching goal of this dissertation and the future work outlined here is to bolster foundational understanding of multifactorial responses to biofeedback in order to advance the development of intentionally designed systems that can improve human mobility and health. Not only does biofeedback training offer an exciting avenue to provide individualized and non-invasive therapy but recent advances in wearable technology and remote sensing present the opportunity to extend biofeedback training outside of traditional clinical spaces and improve the overall accessibility of intervention. The research proposed here will expedite the use of biofeedback as a viable rehabilitation tool and aid in the transition away from inconsistent, invasive therapies as the dominant strategy in CP care. Further, this research may be extended to understand and improve

the consistency of rehabilitation for other populations, such as stroke survivors and individuals with Parkinson's disease and spinal cord injury. Developing strategies that reduce patient burden and simultaneously enhance mobility will shape the future of clinical care and promote long-term independence for individuals following neuromuscular injury.

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APPENDIX

A.1 KINETICS DURING WALKING WITH MOTOR CONTROL-BASED BIOFEEDBACK (CHAPTER 4)

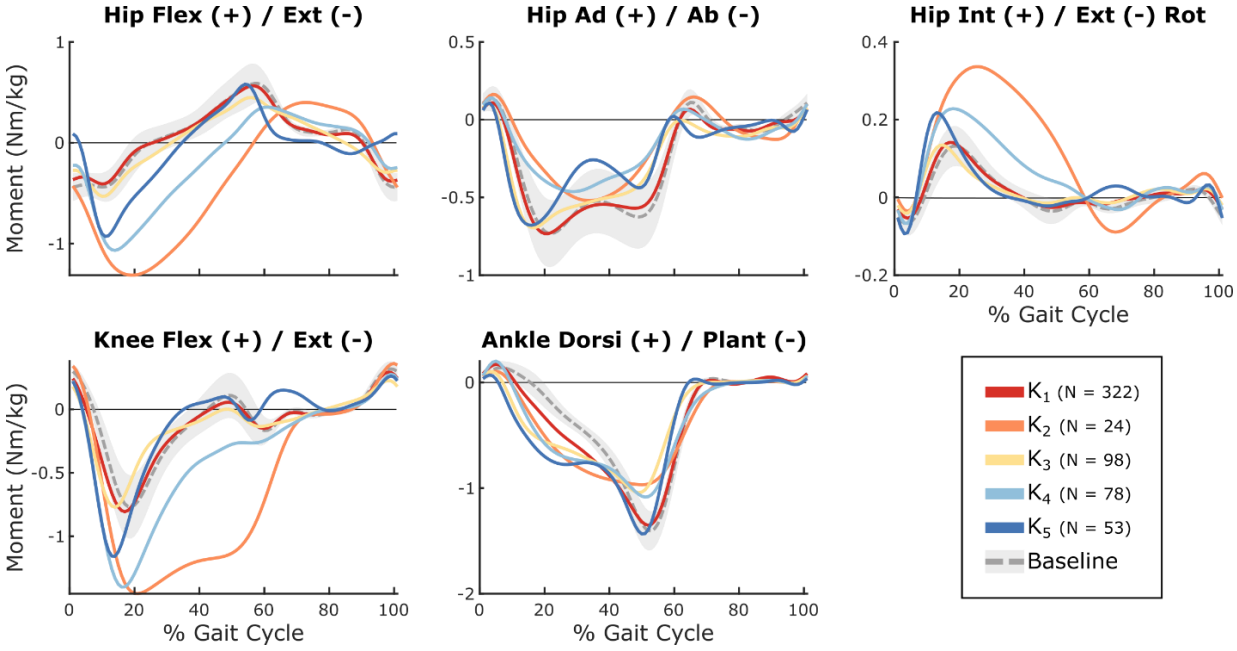

Figure A.1.1 Average hip, knee, and ankle kinetics for the five groups identified by k-means clustering (K_1 to K_5), representing common gait patterns attempted during exploration. The baseline condition shows ± 1SD.

A.2 KINEMATIC CHANGES DURING WALKING WITH MULTIMODAL BIOFEEDBACK (CHAPTER 5)

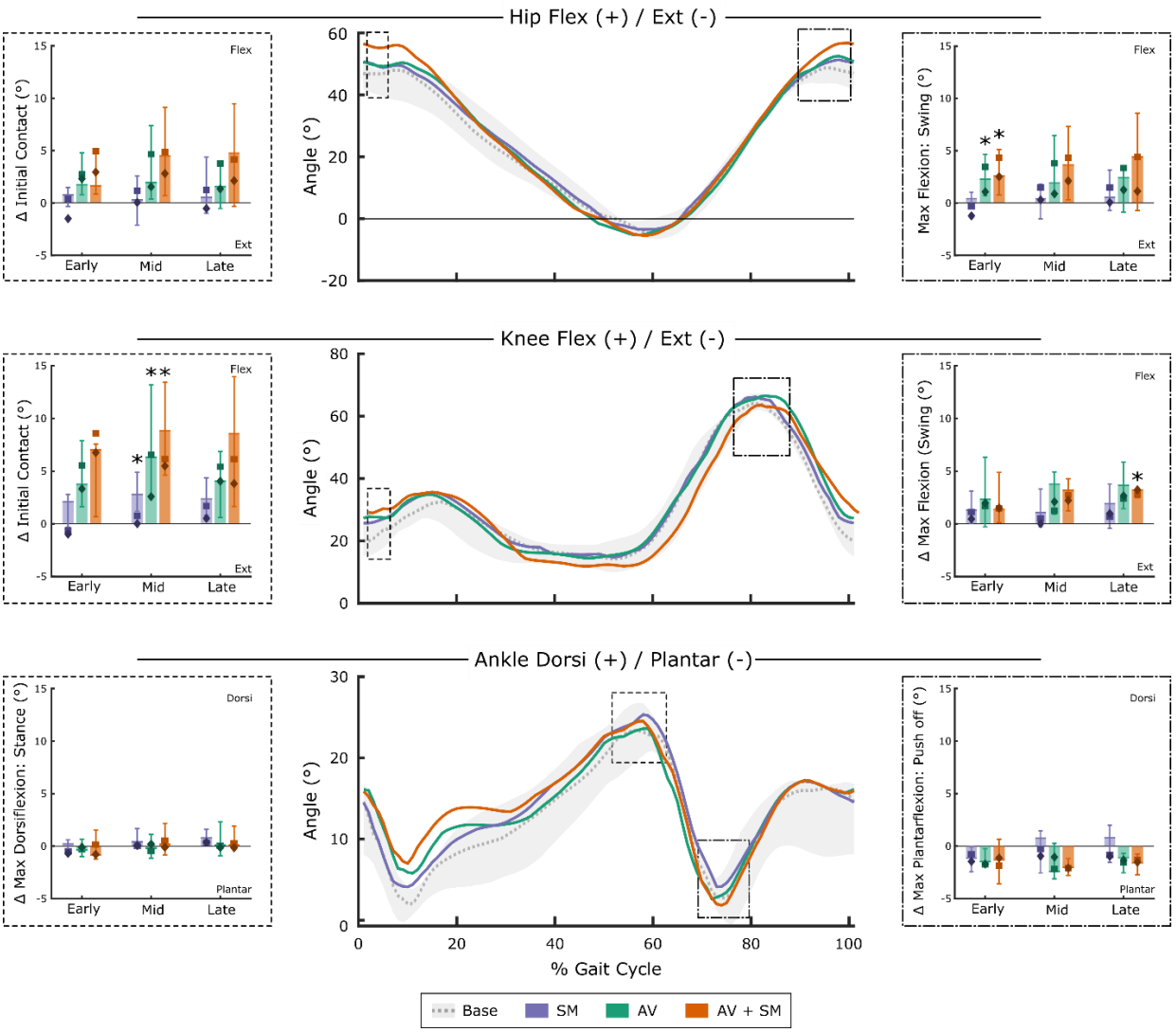

*Figure A.2.1 Sagittal plane kinematics for the hip, knee, and ankle on the less affected limb during walking with sensorimotor (SM), audiovisual (AV) and AV + SM biofeedback. Middle panels show median trends for all biofeedback modalities and baseline during the late phase (strides 181-210) of the pre-acclimation visit. Baseline trends show median (IQR). Bar plots depict median (IQR) changes from baseline for key points within the gait cycle. Initial contact is defined as the mean value over the first 5% of the gait cycle. Median values for post-training (square) and follow-up (diamonds) visits are also presented. Note that because there was inter-participant variability in the timing of maximum angles, there is some discrepancy between the bar plots and median kinematic trends. *denotes significant differences from zero, indicating a change from baseline values ($p < 0.05$; Wilcoxon signed rank tests with Holm-Šídák correction).*