Quantifying Patient-Specific Changes in Neuromuscular Control in Cerebral Palsy

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STUDY PROTOCOL

Background

Current treatments for individuals with cerebral palsy (CP), such as orthopaedic surgery, fail to make significant improvements in gait for 50% of treated patients. CP is caused by an injury to the brain near the time of birth; however, quantifying how this injury contributes to impaired movement remains challenging. We theorize that patient-specific differences in neuromuscular control contribute to the variable and unsatisfactory outcomes after treatment in CP; quantifying these differences is key to understanding and improving pathologic movement. Recent evidence from human and animal studies suggests that control of movement can be described by muscle synergies; low-dimensional, weighted groups of muscles that are consistently activated together in fixed ratios. Synergies are calculated from electromyography (EMG) using matrix factorization algorithms, such as nonnegative matrix factorization (NNMF). During gait, synergies can describe muscle activity in unimpaired individuals. After stroke, even fewer synergies are required, suggesting simplified control that may contribute to impaired movement. In a study of over 500 individuals with CP, we demonstrated that synergy complexity was also reduced compared to unimpaired individuals. Further, our preliminary results suggest that individuals with complex synergies, more similar to unimpaired individuals, are more likely to have good outcomes after a variety of treatments compared to individuals with reduced synergy complexity.

These results motivate our proposed research to use synergies as a framework to quantify altered neuromuscular control in CP and inform treatment planning. There are several important knowledge gaps that need to be addressed to determine the clinical utility of synergy analyses. First, we need to determine if an individual's synergies predict treatment outcomes and provide additional insight beyond traditional tools of clinical motion analysis. Second, we need to establish the adaptability of synergies. EMG is typically only collected before treatment in clinical motion analysis and we do not know if or how neuromuscular control changes after treatment. If synergies can change, new treatment strategies such as biofeedback training may be able to target altered synergies and improve movement. If synergies do not change, we can use an individual's synergies to predict responses to different treatments and identify their "best" possible gait pattern given their neurologic capacity. Finally, from a theoretical perspective, we need to further develop our understanding of the contribution of altered synergies to impaired movement in CP. We developed a new algorithm in OpenSim, an open-source platform for musculoskeletal modeling, which allows users to specify and test different control strategies. We will use this platform to create patient-specific simulations and evaluate how changes in synergies influence muscle recruitment, movement, and energy costs of walking.

The long-term goals of the proposed research are to improve movement and quality of life for individuals with CP. This proposal will determine if quantifying altered neuromuscular control with synergy analysis and musculoskeletal simulation can provide clinicians with new tools to optimize treatment and improve walking ability. Our specific aims are to:

Aim 1: Determine if pre-operative synergies predict outcomes at 12 months after orthopaedic surgery. We will recruit 55 individuals with diplegic cerebral palsy (CP) who are undergoing single-event multi-level orthopaedic surgery (SEMLS) at Gillette for standard of care. Each individual will receive gait analysis including EMG to evaluate synergies before and after surgery, which is part of standard of care. We hypothesize that individuals with more complex synergies (i.e., synergies similar to unimpaired individuals) will have greater improvements in walking kinematics, energy costs, and quality of life 12 months after orthopaedic surgery.

Aim 2: Evaluate stability of synergies with respect to time and treatment. With the same participants as Aim 1, we will compare synergies during gait between two visits before surgery and 6 and 12 months after surgery. This investigation will determine whether synergies are repeatable between days in CP and whether synergies adapt or change in response to surgical changes to the musculoskeletal system.

Human Subjects Involvement, Characteristics, and Design

Aims 1 and 2 will use the same set of subjects to evaluate if synergies predict outcomes after SEMLS (Aim 1) and if synergies change after surgery (Aim 2). We will recruit 55 individuals with CP who have been recommended for surgical treatment at Gillette Children's Specialty Healthcare over three years. Our inclusion criteria for Aims 1 and 2 are: age > 6, diagnosis of spastic diplegic cerebral palsy, GMFCS Levels I-III, absence of dystonia/ataxia/athetosis, no prior surgical procedures, no pharamacological spasticity treatments (*e.g.* botulinum toxin, baclofen, etc.) within 3 months prior to first gait analysis, capacity to follow instructions and provide informed assent, ability to walk across 30 ft. walkway at least 10 times, absence of acute or chronic pain in lower-extremities, and no current pharmacological agents that impact neuromuscular control. Subjects will be recruited who are being evaluated for SEMLS surgery and includes one or more of the following procedures: femoral and tibial derotation osteotomies, surgical lengthening of the gastrocnemius, psoas, hamstrings and adductors, bone and soft tissue alignment of the foot, botulinum toxin injection, distal femoral extension osteotomy, and patellar tendon advancement. Subjects will not be excluded on the basis of ethnic background, race, sex, or socioeconomic factors.

Each subject will receive instrumented gait analysis before and after treatment. Post-operative gait analyses will be at 6 and 12 months to ensure that the patients are ambulatory and to evaluate neuromuscular control over a full year of recovery. Each gait analysis will include kinematics, kinetics, electromyography (EMG), and a physical exam. EMG will be collected for 5 muscles on each leg. Subjects will perform a minimum of 5 trials walking across the laboratory at each visit. The physical exam will be completed by an experienced pediatric physical therapist and include evaluations of range of motion, spasticity (Modified Ashworth Score, Tardieu Scale, and instrumented spasticity measurement system), selective motor control (SCALE), manual muscle strength, and bone alignment.

a. <u>Potential risks:</u>

There are minor risks associated with completing motion analysis during gait; however, these risks are not greater than minimal risk and are similar to activities of daily living. Tripping and falling are possibilities and we will take numerous precautions to prevent such risk, as described below. Fatigue and muscle soreness are also potential risks and we will provide adequate time to rest and recover for all tasks.

b. <u>Recruitment and informed consent:</u>

Children with cerebral palsy will be recruited from Gillette Children's Specialty Healthcare using brochures designed to describe the research and involvement. An experienced research coordinator will assist with recruiting and contacting potential participants. Before gait analysis, each subject will receive a thorough explanation of the protocols from a member of the research team. We will obtain informed permission from the parent or guardian and assent from the child.

Children that do not voluntarily communicate their assent and understand the procedures will not be included in the study. Information will be provided verbally and in writing. Subjects will be reassured of their right to withdraw at any time from the study.

c. Protection against risks:

We take numerous precautions to protect against risks associated with using motion capture to analyze human movement. To prevent tripping and falling we ensure that the floor of the lab is free from wires or other obstructions. Additionally, we can provide additional support through harnesses, bracing, or walking beside the subject, if necessary. Electromyography is also safe and has been tested and used extensively during gait and similar tasks. We will inspect all wires and connections before every experiment. Subjects will be given frequent breaks during all experiments to avoid fatigue. For all experiments, subjects can terminate the experiment at any time. To protect against any breach in confidentiality, data collected for this study will be stored securely on password-protected computers. Codes instead of names of subjects will be used on all data files and reports. Any data used for publication or presentations will be de-identified.

d. Potential benefits of the proposed research to human subjects and others:

There are no immediate potential benefits to the participants in this study.

e. Importance of the knowledge to be obtained:

The potential risks associated with this study are reasonable in the context of the knowledge and advancement in our understanding of cerebral palsy that will be gained. We anticipate that the proposed experiments will provide a new framework for quantifying altered neuromuscular control in cerebral palsy and improving treatment planning. This research will provide insight into the impact of orthopaedic surgery and evaluate the potential of using measures of altered neuromuscular control to predict outcomes. The results from this work will also be extendable to other clinical populations such as stroke, traumatic brain injury, spinal cord injury, and multiple sclerosis, which also exhibit impaired neuromuscular control.

STATISTICAL ANALYSIS

Aims 1 and 2 prospectively evaluate neuromuscular control among individuals with cerebral palsy who are receiving single-event multi-level orthopaedic surgery (SEMLS) as part of their standard care at Gillette Children's Specialty Healthcare. Our sample size analysis, based upon our prior analyses of synergy complexity repeatability and associations with outcomes, suggest a sample size of 55 subjects for 90% power to detect ½ a standard deviation change in synergy complexity assuming a 20% drop-out rate, alpha = 0.05. This sample size is based upon Aim 2 to detect if synergies change after treatment. In our preliminary analysis, a ½ standard deviation change in synergy complexity (Dynamic Motor Control, DMC) was associated with a 5-point difference in the Gait Deviation Index (GDI), which is generally the threshold for defining a clinically significant improvement in walking ability in clinical motion analysis. We are evaluating synergy complexity using DMC, which we previously evaluated and tested on over 500 children with cerebral palsy and 84 typically-developing children. In this prior research, DMC could differentiate between functional ability levels among individuals with cerebral palsy.

We use causal modeling and Bayesian Additive Regression Trees (Table 1) to evaluate whether pre-operative synergy complexity and structure are associated with changes in GDI after SEMLS at 12 months post-op. We constructed our causal model with a Directed Acyclic Graph (DAG) . The logic behind our DAG is as follows:

1. Our objective was to determine the impact of SEMLS on change in GDI (ΔGDI). Thus, SEMLS is our exposure and ΔGDI is our outcome. SEMLS induces a change in impairments (ΔImp) that causes the observed ΔGDI.
2. The covariates we identified as common causes of both SEMLS and ΔGDI included: Age, baseline GDI (GDI_{pre}), and baseline impairment (Imp_{pre}). Baseline impairments represent a set of variables collected during clinical gait analysis to evaluate neurologic and orthopedic impairments (Table 1).
3. Surgical treatment history (Hx) is a common cause of baseline impairment (Imp_{pre}) and whether or not SEMLS is recommended.
4. We included a general severity (Sev) measure as an unmeasured factor that impacts baseline impairment (Imp_{pre}) and surgical treatment history (Hx).

From the DAG we determined the adjustment set needed (*e.g.,* regression, BART) to evaluate the total causal effect of SEMLS on ΔGDI. For this DAG, the minimal sufficient adjustment set to estimate the total causal effect of SEMLS on ΔGDI was: Age, GDI_{pre}, and Imp_{pre}. We also determined the adjustment set to evaluate the total causal effect of baseline impairment (Imp_{pre}) on ΔGDI and GDI_{pre}. The minimal sufficient adjustments sets were Age and Hx for ΔGDI and Age for GDI_{pre}. The plausibility of a DAG can be evaluated by identifying conditional independencies, variables that should be independent given the causal relationships defined in the DAG. We identified the adjustment sets and independencies with dagitty[4] and all analyses were conducted in R (version 4.1.0)[5].

To assess the total causal effects of SEMLS and baseline impairments (Imp_{pre}) on change in GDI (ΔGDI) we used Bayesian Additive Regression Trees (BART), a machine learning method that uses a boosted ensemble of regression trees for nonparametric function estimation relying on a Bayesian probability model[6]. Like other tree-based regression methods, an advantage of BART is that it can handle nonlinear effects and interactions[7]. For causal modeling, recent work has demonstrated that BART-based models achieve accurate and precise causal predictions[8,9]. For this analysis, we used BART models to estimate ΔGDI using the adjustment sets identified by the DAG. Thus, to identify the impact of SEMLS on ΔGDI, we included the covariates Age,

GDI_{pre}, and Imp_{pre}. Baseline impairments were not available for all participants. Missing data in Imp_{pre} were imputed using multivariate imputation by chained equations (MICE)[10]. We used the *bartMachine* package to implement the analysis[11]. We optimized the hyperparameters for each BART model using 10-fold cross-validation. We report the pseudo-R^2 (*1 – SSE/SST)* for each BART model and used k-fold cross-validation (k = 10) to determine the out-of-sample root mean square error (RMSE).

To assess the relative effects of individual variables from BART, we used accumulated local effect (ALE) analysis[12]. The ALE analysis is similar to a partial dependence plot, but the averaging is done locally to avoid including observations that are unlikely to ever be realized (*e.g.,* someone walking three standard deviations slower than average but with a normal cadence). The ALE plots illustrate the impact of each variable over the range of values for that variable, conditioned on the other covariates in the model. Thus, ALE plots can be useful for examining nonlinear effects identified by BART. For example, the ALE plot can highlight nonlinear effects such as when a variable impacts GDI with a deviation from average (*i.e.,* a U-shaped plot) or when a variable only impacts GDI above or below a certain cut-off (*i.e.,* a step function or discontinuity).

Table 1: Variable definitions

Variable	Description
GDI	Overall measure of the deviation in an individual's kinematics compared to nondisabled peers scaled such that mean(sd) over the nondisabled population is 100(10)[13]. Kinematics were evaluated using marker-based motion analysis and a modified plug-in-gait marker set.
SEMLS	Binary variable indicating whether or not child had single-event multi-level orthopedic surgery, defined as a surgery with two or more orthopedic surgeries on at least one leg.
Hx	Binary list of prior surgical treatments.
Age	Years from birth defined as days/365.25
Impairments	**Spasticity:** Mean modified Ashworth score across plantarflexors, hamstrings, hip adductors, and rectus femoris.
	Strength: Mean manual muscle strength score across hip flexors/extensors, knee flexors/extensors, and ankle dorsiflexors/plantarflexors where 1 is defined as a 'visible or palpable contraction' and 5 is defined as 'full range of motion against gravity'.
	Static Motor Control (SMC): Mean static motor control score across hip abduction, hip flexion, hip extension, knee extension, and ankle plantarflexion where 0 is very little or no control of single joint movement, 1 is impaired voluntary movement at a single joint, and 2 is good voluntary movement at a joint.
	Dynamic Motor Control (DMC): Measure of the complexity of muscle activity during gait evaluated from synergy analysis of EMG data. Complexity is evaluated as the total variance accounted for by one synergy of EMG data during CGA and compared to nondisabled peers scaled such that mean(sd) over the nondisabled population is 100(10)[14,15].
	Torsional Deformity: Femoral anteversion and tibial torsion (bimalleolar axis angle) measured during physical exam.
	Contracture: Measures of joint range of motion from physical exam including maximum ankle dorsiflexion with the knee extended, maximum knee extension, unilateral popliteal angle, and maximum hip extension measured during the Thomas Test.

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Dynamic motor control in patients with CP

Parent Consent Form

Your child is being asked to participate in a research study that will investigate how muscles work together to control movement while walking. Your child is being contacted as a potential participant because your child has cerebral palsy (CP), had a recent gait analysis, and is a candidate for surgery at Gillette Children's Specialty Healthcare.

We ask that you read this form. Please take your time to ask any questions and feel comfortable making a decision whether or not you agree for your child to be in the study.

This study is being conducted by Michael Schwartz, Ph.D. from the Center for Gait and Motion Analysis at Gillette and Dr. Katherine Steele, PhD from the University of Washington.

Before you learn about the study, it is important you know the following:

- You and your child's participation is completely voluntary.
- You and your child may not directly benefit by participating in the study but knowledge gained from your participation may help others.
- You or your child's decision to participate or not to participate will not affect your clinical care in any way at Gillette.

Study Purpose

The goal of this study is to better understand how muscles function together as children with CP walk. In particular, we are interested in whether the ability to control muscle activity influences outcomes, and whether this ability is affected by treatment. We think that if a child has good neuromuscular control, they will have a better outcome following surgery but sometimes this control is hard to measure. We want to develop a system that measures motor control reliably and easily so that clinicians can make better treatment decisions and improve the health of our patients. This study will use three dimensional motion capture and muscle activity data collected during gait analyses.

Study Procedures

If you agree to allow your child to participate in this study, your child will complete additional gait analyses before and/or after their standard-of-care surgery. At approximately 12 months after surgery, they will undergo a full gait analysis, similarly to their recent gait analysis. At 6 months after surgery, they will undergo a shorter gait analysis. Some participants will also undergo this shorter gait analysis prior to their surgery.

Risks of Study Participation
Because we will collecting identifiable information (*e.g.* child's name, medical record number), there may be a risk of losing confidentiality. The data we collect will be stored as part of your child's medical record.

Benefits of Study Participation
The gait analysis 12 months after surgery is typically requested as part of your child's standard of care. Study funds will cover this cost. In the future, this research may lead to a better understanding of neuromuscular control in patients with CP and how this affects their outcomes following surgery.

Alternatives to Study Participation
This study is completely voluntary. The alternative is not to participate. If you and your child do not participate it will not impact your relationship with Gillette Children's Specialty Healthcare in any way.

Study Costs/Compensation
Your child will receive a gift card after each research visit. All costs associated with each additional gait analysis are covered by study funds.

Confidentiality
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you or your child as a participant. However, your child's record for the study may be reviewed by departments at Gillette or researchers at the University of Washington with appropriate regulatory oversight for human subject studies. All information collected for the study will be stored in a secured Gillette Children's Specialty Healthcare database. To these extents, confidentiality is not absolute.

Voluntary Nature of the Study
Participation in this study is voluntary. Your decision whether or not to allow your child to participate will not affect your current or future relationship with Gillette. If you decide to participate, you or your child are free to withdraw at any time without affecting these relationships.

Care of Subject in Case of Accident
In the event that this research activity results in injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that your child has suffered a research related injury, let study staff know right away.

Contacts and Questions

The Gillette researcher conducting this study is Michael Schwartz, PhD and the research is coordinated by Meghan Munger, MPH, CCRC. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact Michael at 612-229-3929 (mschwartz@gillettechildrens.com) or Meghan at 612-229-1757 (meghanemunger@gillettechildrens.com).

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the *Patient Representative of the Quality Improvement Resources Department* at Gillette Children's Specialty Healthcare, 200 East University Ave, St. Paul MN 55101, Telephone 651-229-1706 or 1-800-719-4040 (toll free) or email qualityrep@gillettechildrens.com. You may also send feedback by going to https://www.gillettechildrens.org/contact-us/ and completing the feedback form.

You will be offered a copy of this form for your records.

Statement of Consent

I have read the above information. The research project and procedures have been explained to me. I have asked questions and have received answers. I consent to have my child participate in the study. I will receive a signed copy of this consent form for my records. I am not giving up any legal rights by signing this form.

_____ Date: _____

Signature of Parent or Legal Representative

_____

Printed Name of Person Consenting

_____ Date: _____

Signature of Person Obtaining Consent

Statement of Consent for Participants Who Reach the Age of Majority

The participant turned 18 years old during their involvement in this study. I have reviewed study information and consent to continue my participation.

_____ Date: _____

Signature of Participant