# Predictors of Response to an Intensive Bimanual Intervention in Children Living with Cerebral Palsy

Principal investigator: MERCIER, Catherine
Researcher, CIRRIS
Professor, Université Laval
525 boul. Hamel
Québec, QC
G1V 2P3
catherine.mercier@rea.ulaval.ca
418-529-9141 ext. 6701

Co-investigators: FLAMAND, Véronique (CIRRIS, U. Laval)
ROBERT, Maxime (CIRRIS, U. Laval)
CAMPEAU-LECOURS, Alexandre (CIRRIS, U. Laval)
CROTEAU, Émilie (CIUSSS Capitale-Nationale)

# 1. Introduction

Cerebral palsy (CP) is a group of permanent disorders that affect movement and posture development, leading to activity limitations due to damage occurring in the developing brain of the fetus or infant (Cans C., 2000; Oskoui et al., 2013; Rosenbaum et al., 2007). With 2 to 3 children affected per 1,000 live births, CP is the most common disability in childhood. Motor disorders related to CP are often accompanied by sensory, cognitive, perceptive, communication, and behavioural disorders. The most predominant type of CP is hemiparesis: a more pronounced motor impairment on one side of the body. Although motor deficits predominantly affect one of the upper limbs, bimanual coordination deficits are also observed. These bimanual coordination deficits are often more profound than expected based on the deficits of the most affected upper limb (Gordon et al., 2013)· Since most activities of daily living (ADL) require the use of both hands in a coordinated manner, deficits in bilateral coordination have a direct impact on ADL.

Seeking to improve upper limb function, several studies have assessed intensive rehabilitation approaches that are based on motor learning principles and performed in a group context (Novak et al., 2013). Moreover, one study shows that task-oriented training that requires a high number of repetitions and a progression in task requirements improves motor control and manual function (Gordon et al., 2013). The two most studied approaches – constraint-induced therapy and intensive bimanual therapy – show comparable short- and long-term (6 months) outcomes in terms of unimanual and bimanual skills (Gordon et al., 2011). However, results also suggest that bimanual therapy provides larger gains in terms of performance and satisfaction in functional activities (subjectively measured with the Canadian Occupational Performance Measure), potentially because this approach focuses on bimanual activities with the spontaneous use of the most affected arm (de Brito Brandão et al., 2012; Gordon et al., 2011). That said, while self-reported measures provide relevant information about subjects' own perception of their abilities, these measures are subject to many biases (i.e., social desirability) (Waddell & Lang, 2018). *Changes in spontaneous use of the most affected limb in activities of daily living that follow interventions are rarely examined objectively, so the link between improvements measured through clinical evaluations or laboratory tests and any spontaneous use of the most affected limb remains to be definitively established.* This issue is of particular importance considering the Developmental Disregard theory, which suggests that the more affected side is often overlooked during child development since a child learns to prioritize using their healthy side (Taub et al., 2006; Zielinski et al., 2014). As a result, the benefits an intervention may have on motor performance can be different when we compare on-demand tasks and spontaneous use in ADL. Based on this theory, improving spontaneous use of the most affected limb might provide better long-term gains than improving motor performance. The development of small wireless motion sensors (accelerometry) now makes it possible to quantify the relative use of each upper limb. A recent study has validated the use of such sensors (ActiGraph) to assess spontaneous movements of upper limbs in ADL in children with hemiplegic cerebral palsy (Dawe et al., 2019) ). These advances pave the way for a quantitative characterization of the impact of intensive bimanual therapy in children's daily living.

Another important challenge that researchers and clinicians presently face in implementing interventions is the heterogeneity of the population of children living with cerebral palsy, and the variability observed in response to interventions. The heterogeneous nature of brain damage that results in cerebral palsy may be a crucial factor in explaining variability in response to treatment. However, biomarkers derived from magnetic resonance imaging (MRI) – such as the timing when the lesion occurred, as well as its extent and precise location – only moderately predict effects on sensorimotor functions (Feys et al., 2010; Holmefur et al., 2013). One of the reasons for this is that the brain is still highly plastic at this stage of development, which allows for significant “re-wiring” that may deviate from what is observed in typically developing children. Characterizing this re-wiring could be useful at a clinical level: the identification of specific biomarkers may help clinicians customize interventions according to individual characteristics (Jaspers et al., 2015) . For example, it has been shown that brain damage can interfere with the phenomenon of withdrawal of ipsilateral corticospinal projections normally occurring during development, especially if it occurs between the $24^{th}$ and $34^{th}$ week of gestation (Staudt et al., 2004) . As a result, some children will demonstrate ipsilateral control of the most affected hand (or mixed control, rather than contralateral control). The presence of ipsilateral control, as demonstrated for example in transcranial magnetic stimulation (TMS), is typically associated with poorer motor function (Holmström et al., 2010; Mackey et al., 2014; Staudt, 2002; van der Aa et al., 2013) . The structural integrity of the corticospinal pathway between the injured hemisphere and the most affected hand, based on diffusion tensor imaging (DTI) measurements, has also been reported to be associated with motor function (Bleyenheuft et al., 2007; Friel et al., 2014; Glenn et al., 2007; Gupta et al., 2017; Holmström et al., 2011; Hung et al., 2019; Kuczynski, Dukelow, et al., 2018; Mackey et al., 2014; Marneweck et al., 2018; Nemanich et al., 2019; Smorenburg et al., 2017).

Despite established relationships between neuroanatomical or neurophysiological markers and motor function of the most affected upper limb, few studies have been able to establish links between these markers and the response to specific interventions (Robert et al., 2021; Rocca et al., 2013) . Several reasons may explain these inconsistent results: On the one hand, there are inherent limitations of neuroimaging approaches that target specific structures (e.g., corticospinal pathway, corpus callosum, etc.). The use of multiple metrics in one study could help us understand the complexity of brain reorganization (e.g., the importance of the integrity of the corticospinal pathway between the affected hemisphere and the most affected hand may depend on the presence of a predominantly ipsilateral or contralateral reorganisation of the corticospinal pathway). On the other hand, these results are usually related to changes in complex functional tasks, which require many brain structures and processes. Although the goal of rehabilitation is ultimately to improve motor function in the context of ADL, the standardized assessment of mediating variables (intermediate between two other variables and less complex than the use of the upper limb in ADL) that focused on a specific function, can be an interesting way to bridge the gap between neuroanatomical/neurophysiological variables and complex motor functions. *The use of more precise assessments of uni- and bilateral sensorimotor control, as made possible by the development of robotic upper limb assessment systems, could clarify the relationship between neuroanatomical/neurophysiological variables and clinical improvements.* This approach could lead to a better understanding of the variability observed in response to interventions, and ultimately to predicting the effectiveness of interventions based on key biomarkers.

# 2. Objectives and hypothesis

- ***Main objective of the study***

To understand the impacts of an intensive bimanual therapy on uni- and bimanual motor functions and on the spontaneous use of the most affected arm, by clarifying what are the underlying neurophysiological mechanisms involved.

- ***Specific objective 1***

To describe changes that occur in motor function (uni- and bimanual) and in the spontaneous use of the most affected limb following intensive bimanual therapy.

*Hypothesis 1.1:* Improvements of uni- and bilateral motor function will be observed both following the intervention and at 6 months follow-up.

*Hypothesis 1.2:* Improvements of spontaneous use of the most affected limb will be observed both following the intervention and at 6 months follow-up.

- ***Specific objective 2***

To assess the relationship between uni- and bilateral motor changes, spontaneous use of the most affected limb, and self-reported changes. Potential covariables (for example proprioception) will also be evaluated.

*Hypothesis 2.1:* Immediately after the intervention, improvements of bilateral motor function will be observed using clinical and robotic assessments. These evaluations will better predict changes in the spontaneous use of the most affected limb in the context of ADL than evaluations of unilateral motor function do.

*Hypothesis 2.2:* The long-lasting effect of the intervention (6-month follow up vs. post-intervention evaluation) will be predicted by improvements during the intervention (post vs. pre-evaluation).

*Hypothesis 2.3:* At the 6-month follow-up, changes in spontaneous use of the most affected limb will be moderately associated with self-reported changes.

- ***Specific objective 3***

To explore predictive value of neuroimaging variables evaluated in pre-intervention on motor function changes (uni- and bilateral).

*Hypothesis 3:* The integrity of the corpus callosum will be a predictor of changes in bilateral performance, with a lower integrity being associated with smaller gains.

- ***Specific objective 4***

To compare the changes observed during a first exposure to intensive bimanual therapy with changes observed during a subsequent exposure.

*Hypothesis 4:* The beneficial effects of a subsequent exposure to the bimanual therapy will be identical to those observed during the first exposure (i.e., no ceiling effect will be observed).

# 3. Methodology

- ***Research design***

The experimental design is presented in Figure 1. All participants will receive an intensive bimanual therapy of a total of 60 hours over a two-week period. Evaluations will be performed before, immediately after, and 6 months after the intervention. All participants will be invited to repeat the intensive bimanual therapy camp on subsequent years if they wish to, if they meet the inclusion criteria.

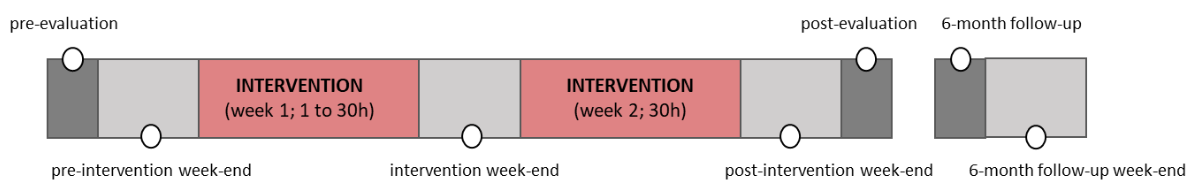


**Figure 1**. Experimental design

- ***Participants***

Thirty children living with cerebral palsy will be recruited over a 5-year period for a first participation in an intensive bimanual therapy camp. Several recruitment approaches will be used, including clinical programs, websites, and social media.

*Selection criteria:*

(1) being aged between 6 and 17 years old;
(2) having a diagnosis of cerebral palsy or spastic hemiparesis encephalopathy;
(3) having sensorimotor deficits of one or both upper limbs (spastic hemiparesis with a dominance on one side of the body; *Manual Ability Classification System* (MACS) level 1, 2 or 3);
(4) having the cognitive capacity to understand and perform tasks in the study.

*Exclusion criteria:*

(1) presenting other significant health problems that may interfere with requested tasks or with clinical interventions;
(2) having had a Botox injection in one or both upper limb(s) with the 4 months prior to the bimanual therapy intervention;
(3) presenting uncorrected visual deficits.

N.B. Having a ferromagnetic implant is not an exclusion criterion; any such participants will be eligible but will not be required to perform the MRI.

*Participants recruited for specific objective 4*

Children who have already participated in this bimanual therapy once will be eligible to participate in the therapy again, assuming they still meet the inclusion criteria.

- ***Summary of the intervention***

Children will participate in an intensive bimanual therapy session of 6 hours of therapy per day, 5 days a week, for a period of two weeks (so the intervention's total duration is of 60 hours of bimanual therapy). The camp will be held every year at the PEPS at Université Laval, in Quebec City, Canada. Each child will be paired with the same therapy worker throughout the camp (1:1 ratio). The therapy workers will be students in health programs (occupational therapy, physiotherapy, and kinesiology) or graduate students in clinical research at Université Laval. A mandatory training will be offered to all students in order to ensure that the strategies used for bimanual activities are standardised; safety protocols and data collection will be also addressed during the training. At least one occupational therapist will always be present on-site to supervise the student therapy workers and the activities (i.e., board games, arts and crafts, basic cooking, etc.). Detailed information related to how intensive bimanual therapy is developed and conducted can be found in (Charles & Gordon, 2006).

- ***Evaluations***

There will be three periods of evaluation (pre-intervention, post-intervention, and 6-month follow-up).

**Table 1**. Summary and planning of the evaluation

| **Evaluations** | | **Pre-intervention** | **During the intervention** | **Post-intervention** | **6-month follow-up** |
|---|---|---|---|---|---|
| Neurophysiological evaluation | MRI/DTI* | ✓ | | | |
| Robotic evaluation | KINARM | ✓ | | ✓ | ✓ |
| Spontaneous use | Accelerometry | ✓ | ✓ | ✓ | ✓ |
| Clinical evaluation | TPDT | ✓ | | ✓ | ✓ |
| | JTTHF | ✓ | | ✓ | ✓ |
| | BBT | ✓ | | ✓ | ✓ |
| | AHA | ✓ | | ✓ | ✓ |
| | TACT | ✓ | | ✓ | ✓ |
| | MVPT-R | ✓ | | ✓ | ✓ |
| Self-assessments | CHEQ | ✓ | | ✓ | ✓ |
| | COPM | ✓ | | ✓ | ✓ |

MRI: *Magnetic Resonance Imaging*; DTI: *Diffusion Tensor Imaging*; JTTHF: *Jebsen Taylor Test of Hand Function;* BBT: *Box and Block Test*; AHA: *Assisting Hand Assessment*; TACT: *Two-Arm Coordination Test;* MVPT-R: *Motor-Free Visual Perception Test–Revised;* CHEQ: *Children's Hand-use Experience Questionnaire;* COPM: *Canadian Occupational Performance Measure*. *MRI will be performed only in the first participation in the bimanual therapy.

*Neuroimaging evaluation*

Each child will undergo a magnetic resonance imaging (MRI) test prior to the pre-intervention, with the exception of children presenting a contraindication to MRI and/or children who have already participated in the therapy camp once (Objective 4) and so have already provided MRI test results.

The diffusion tensor imaging (DTI) technique will be used for the pre-evaluation MRI. That will make it possible to assess the integrity of several neuroanatomical structures (i.e., corpus callosum, corticospinal pathways, etc.). The tractography of neuroanatomical pathways will be reconstructed using the Continuous Tracking method (Mori et al., 1999)  In order to assess the integrity of neuroanatomical motor structures (e.g., corpus callosum, ascending and descending sensorimotor pathways) (Robert et al., 2021), the diffusion analysis will be done using the TractoFlow processing pipeline (Garyfallidis et al., 2014; Theaud et al., 2020).

*Robotic evaluation*

Four standardized sensorimotor tasks will be performed using a Kinarm Exoskeleton Lab (Kinarm, Kingston, ON Canada) in a randomized order for a total duration of approximately 45 minutes (including installation and calibration). This system allows for the execution of upper limb tasks on the horizontal plane while recording upper limb kinematics and tracking eye movements. The metrological properties of these tasks have been assessed in adults and children with hemiparesis (see the description of each task).

In the unilateral task **Visually Guided Reaching**, the child must point at 4 targets as quickly and accurately as possible. The targets are spread out over a radius of 10 cm from the starting target, and are presented in a pseudo-random order (for total of 32 reaching movements) (Coderre et al., n.d.; Kuczynski, Dukelow, et al., 2018; Kuczynski, Kirton, et al., 2018). The two upper limbs will be evaluated successively.

In the bilateral task **Object Hit**, balls move from the distal part of the screen to the proximal part (i.e., towards the child) in different medial-lateral positions (Tyryshkin et al., 2014). Child must hit the balls with the hand of their choice, with each successful contact generating haptic feedback. Three hundred balls are presented at a speed that gradually increases as the task progresses.

In the bilateral task **Ball on the Bar**, a virtual bar is put into the hands of the subject, and a virtual ball is placed on the bar (R Lowrey, 2014). Four targets are successively presented to the child, whose objective is to move the ball into each target as quickly and accurately as possible. The task has 3 levels of one minute's duration. At levels 2 and 3, the ball can “roll” and fall off the bar, which requires precise bilateral control.

In the proprioception task **Arm-Position Matching**, the child's sense of upper limb position is evaluated (Dukelow et al., 2010; Kuczynski, Dukelow, et al., 2018; Kuczynski et al., 2017). The Kinarm moves one of the more affected upper limb passively to a predetermined position. The child must then move their contralateral limb to match the position of the limb in the other hemi-space without any visual feedback. Four different positions are tested for a total of 7 times each.

*Spontaneous use*

Inertial control units (ActiGraph GT9X-BT Link, ActiGraph, Florida, FL; 3.5 cm 3.5 cm 1 cm, 14 g) worn on both wrists (Velcro bracelets from the company) will be used to assess spontaneous use of the most affected arm, with respect to the use of the less affected arm. The validity of this type of sensor is good (agreement >81%) based on results of studies that compared accelerometer data to video observations in children living with cerebral palsy (Beani et al., 2019; Dawe et al., 2019) . In our case, sensors will be worn for 4 weekends (before, during, immediately after, and 6 months after the intervention) as well as for two days (one per week) during the intervention. While data will be measured during the interventions, the majority of data will be collected exclusively on weekends in an effort to minimize differences between school attendance and holiday periods. The ActiGraph data will be collected in 3 axes at 100 Hz, and then analyzed as vectors with the ActiLife v.6.13.4 software (ActiGraph, Pensacola, FL). Unilateral and bilateral functions will be quantified by summing up the activities detected at the upper limbs, which makes it possible to obtain use ratios for each limb.

*Clinical evaluation*

The ***Two-Point Discrimination Test*** (***TPDT***) at a distance of 3 mm is the most sensitive test there is to determine tactile threshold in children with spastic hemiplegia (Krumlinde-Sundholm & Eliasson, 2002). Only the pulp of the fingers will be evaluated, starting with the less-affected hand. A successful trial will be considered to be 5 consecutive successes out of 10 attempts, since children often need more testing to understand what they are seeking to detect as sensation (Krumlinde-Sundholm & Eliasson, 2002) . If a child is not able to distinguish between 2 static points spaced at 3 mm distance (the standard for the tactile threshold), the test will be repeated with a distance of 7 mm between the 2 static points. This test is valid and accurate in children living with cerebral palsy (Bolanos et al., 1989).

The ***Jebsen Taylor Test of Hand Function*** (***JTTHF***) is used to evaluate the unimanual function. This test consists of 7 standardized tasks, performed first with the non-dominant hand and then with the dominant hand (Jebsen et al., 1969). In this project, only the first 6 tasks will be used. For each task, the score is the time required to complete the task, in seconds (a maximum of 120 seconds is allocated per task). The total score is the sum of time for all six tasks. Test fidelity is good in children with stable manual impairment (range of intraclass correlation coefficients (ICC) is between 0.88-0.97 for the dominant hand and 0.95-0.99 for the non-dominant hand, depending on the task) (Taylor et al., 1973). No learning effect has been detected (Jebsen et al., 1969).

The ***Box and Blocks Test*** (***BBT***) is a standardized, validated test that measures manual dexterity. In this test, the child must take one block at a time with one hand, then transfer it to the other side of the box (across a middle line) (Mulcahey et al., 2012). The score is the number of blocks moved in 60 seconds. Normative values for children with typical development are available, and the CCI is 0.85 for test-retest fidelity, and 0.99 for inter-evaluator fidelity (Platz et al., 2005).

The ***Assisting Hand Assessment*** (*AHA*) (Krumlinde-Sundholm et al., 2007) evaluates how effectively the most affected limb assists the dominant hand in bimanual tasks. This test consists of standardized tasks with toys that are used during a semi-structured game session. The test is video-recorded, and the video is analyzed and scored later. The AHA was designed and validated specifically to measure bimanual performance in children with hemiparesis (cerebral palsy of the spastic hemiparesis type, or with brachial plexus resulting in unilateral damage to the upper limb). The AHA has excellent fidelity (ICC 0.97 for inter-evaluator and ICC 0.99 for intra-evaluator) and sensitivity to change (Holmefur et al., n.d.; Krumlinde-Sundholm et al., 2007). The game session takes 15-20 minutes. Results are scored in logit-based AHA-units (maximum score 100). The evaluator must be certified to administer, score, and analyze this evaluation.

The ***Two-Arm Coordination Test*** (***TACT***) evaluates the constrained bilateral use of both upper limbs, using an electronic tracking device (eight tests; four clockwise and four counter-clockwise). This device has been validated with people living with cerebral palsy (Riquelme et al., 2019). The variables are time and number of errors.

The ***Motor-Free Visual Perception Test–Revised*** (***MVPT-R***) is a visual perception test that assesses consistency of form, spatial orientation, discrimination, memory, and visual closure. This test was validated with people living with cerebral palsy (Tsai et al., 2009).

*Self-assessments*

Questionnaires related to daily-living activities will be completed both pre- and post-intervention, as well as at the follow-up 6 months later.

The ***Children's Hand-use Experience Questionnaire*** (***CHEQ***) consists of 29 questions designed to evaluate how the most-affected upper limb is used in ADL (Sköld et al., 2011). The questionnaire presents a list of everyday life activities that are usually carried out with both hands; the child and the parents rate the time required to accomplish the task, the effectiveness of the child's grip, and how hampered they felt in the task. A web version of the questionnaire is available and has been validated (test-retest fidelity for all 3 scales: CCI 0.88- 0.91) in children with spastic hemiparesis cerebral palsy (Amer et al., 2016).

The ***Canadian Occupational Performance Measure*** (***COPM***) will be administered both pre- and post-intervention, as well as at the 6-month follow-up. Pre-intervention COPM will make it possible to identify bilateral activities that the child wants to improve (Law et al., 1990) and the child and their parents will establish current performance and satisfaction scores for these activities. After the intervention, they will again establish performance and satisfaction scores for the activities initially identified (a 2-point change is considered clinically significant with this measure) (Verkerk et al., 2006). COPM is a well-established measurement tool, valid, faithful and responsive to changes. This tool measures the functional changes perceived by the client and provides an indication of how the clinical setting have been transferred to daily life (Carswell et al., 2004).

- ***Statistical analysis***

For objectives 1, 2 and 4, in addition to descriptive statistics (mean or median), a general (or generalized if the assumptions of normality are not met), linear mixed model (GLMM) with maximum likelihood estimates will be used. GLMM provides flexibility to examine the effect of categorical and continuous independent variables (and their interactions) within and across related observation groups, and robustness to missing data. In this study, data are sampled in a multi-stage manner (children are nested within recruitment cohorts), and ignoring this clustering will lead to the violation of the independence of the residuals and the underestimation of the parameters of the statistical model(McNeish & Stapleton, 2016). However, GLMM requires large sample size. Due to financial costs (2-week intervention across five years with one therapy worker per child) and recruitment difficulties, it is not possible to go beyond 30 participants. Therefore, a bootstrap method (i.e., a statistical procedure that resamples a single dataset to create many simulated samples) will be applied to meet the assumptions of GLMM.

Objective 1&4 – Participants and Cohorts will be set as random effects, Time (pre- post- 6-months) and Exposition (first year, second year, etc.) and their interaction will be set as fixed effects.

Objective 2 – Participants and Cohorts will be set as random effects, Time (pre- post- and 6-months), uni- and bi-lateral Motor functions and their interaction as fixed effects.

Objective 3 - Correlational analyses (Pearson or Spearman) will be performed between corpus callosum integrity (measured by MRI/DTI) and changes in variable of bilateral motor tasks (measured by robotic evaluation).
Given that children will be aged from 6 to 17, the potential effect of age on the different variables will be explored to determine the relevance of including age as a covariate in some analyses. However, it has been proved recently that age is not associated with different measures obtained by DTI in youth with cerebral palsy, contrary to what is observed in youth with a typical development (Papadelis, Kaye et al. 2019). Moreover, when normative data is available, tests results will be converted to z-score to minimize the impact of age and sex.
P-values will be corrected for multiple testing using the Benjamini and Hochberg False Discovery Rate.

- ***Limitations of the methodology***

The main limitation of the study will be its limited sample size: It is expected that the sample will be heterogeneous in terms of age and clinical criteria. This is a common limitation for studies in this area. A multimodal approach to assess intra-participant changes will be used to minimize the impact of these limitations.

Another limitation is the restricted time for accelerometry measurements (2 days for each time point). One-week periods are generally preferred in studies conducted in adults. The choice was made here to restrict measurements to weekends in order to reduce biases related to ADL differences between schooldays and holidays (especially for the 6-month follow-up). This option was also selected to yield greater acceptability among the children (since they must wear the devices for four separate periods totalling 8 days of time).

The use of GLMM with a small sample size is another limitation. However, a bootstrap technique will be used. This method does not create any data and the estimated parameters might not reflect with precision the parameters of the population, which is not a major issue in this project.

Finally, it is important to underscore that the goal of this study is not to determine the effectiveness of intensive bimanual interventions: this has already been established by previous studies (Novak et al., 2013; O'Connor et al., 2016; Peters et al., 2019; Shierk et al., 2016), which is why no control group was included here.

# Bibliography

Amer, A., Eliasson, A.-C., Peny-Dahlstrand, M., & Hermansson, L. (2016). Validity and test-retest reliability of Children's Hand-use Experience Questionnaire in children with unilateral cerebral palsy. *Developmental Medicine and Child Neurology*, *58*(7), 743–749. https://doi.org/10.1111/dmcn.12991

Beani, E., Maselli, M., Sicola, E., Perazza, S., Cecchi, F., Dario, P., Braito, I., Boyd, R., Cioni, G., & Sgandurra, G. (2019). Actigraph assessment for measuring upper limb activity in unilateral cerebral palsy. *Journal of Neuroengineering and Rehabilitation*, *16*(1), 30. https://doi.org/10.1186/s12984-019-0499-7

Bleyenheuft, Y., Grandin, C. B., Cosnard, G., Olivier, E., & Thonnard, J.-L. (2007). Corticospinal dysgenesis and upper-limb deficits in congenital hemiplegia: a diffusion tensor imaging study. *Pediatrics*, *120*(6), e1502-11. https://doi.org/10.1542/peds.2007-0394

Bolanos, A. A., Bleck, E. E., Firestone, P., & Young, L. (1989). Comparison of stereognosis and two-point discrimination testing of the hands of children with cerebral palsy. *Developmental Medicine and Child Neurology*, *31*(3), 371–376. https://doi.org/10.1111/j.1469-8749.1989.tb04006.x

Cans C. (2000). Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Developmental Medicine and Child Neurology*, *42*(12), 816–824. https://doi.org/10.1017/s0012162200001511

Carswell, A., McColl, M. A., Baptiste, S., Law, M., Polatajko, H., & Pollock, N. (2004). The Canadian Occupational Performance Measure: a research and clinical literature review. *Canadian Journal of Occupational Therapy. Revue Canadienne d'ergotherapie*, *71*(4), 210–222. https://doi.org/10.1177/000841740407100406

Charles, J., & Gordon, A. M. (2006). Development of hand-arm bimanual intensive training (HABIT) for improving bimanual coordination in children with hemiplegic cerebral palsy. *Developmental Medicine and Child Neurology*, *48*(11), 931–936. https://doi.org/10.1017/S0012162206002039

Coderre, A. M., Zeid, A. A., Dukelow, S. P., Demmer, M. J., Moore, K. D., Demers, M. J., Bretzke, H., Herter, T. M., Glasgow, J. I., Norman, K. E., Bagg, S. D., & Scott, S. H. (n.d.). Assessment of upper-limb sensorimotor function of subacute stroke patients using visually guided reaching. *Neurorehabilitation and Neural Repair*, *24*(6), 528–541. https://doi.org/10.1177/1545968309356091

Dawe, J., Yang, J. F., Fehlings, D., Likitlersuang, J., Rumney, P., Zariffa, J., & Musselman, K. E. (2019). Validating Accelerometry as a Measure of Arm Movement for Children With Hemiplegic Cerebral Palsy. *Physical Therapy*, *99*(6), 721–729. https://doi.org/10.1093/ptj/pzz022

de Brito Brandão, M., Gordon, A. M., & Mancini, M. C. (2012). Functional impact of constraint therapy and bimanual training in children with cerebral palsy: a randomized controlled trial. *The American Journal of Occupational Therapy : Official Publication of the American Occupational Therapy Association*, *66*(6), 672–681. https://doi.org/10.5014/ajot.2012.004622

Dukelow, S. P., Herter, T. M., Moore, K. D., Demers, M. J., Glasgow, J. I., Bagg, S. D., Norman, K. E., & Scott, S. H. (2010). Quantitative assessment of limb position sense following stroke. *Neurorehabilitation and Neural Repair*, *24*(2), 178–187. https://doi.org/10.1177/1545968309345267

Feys, H., Eyssen, M., Jaspers, E., Klingels, K., Desloovere, K., Molenaers, G., & de Cock, P. (2010). Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. *European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society*, *14*(2), 169–177. https://doi.org/10.1016/j.ejpn.2009.01.004

Friel, K. M., Kuo, H.-C., Carmel, J. B., Rowny, S. B., & Gordon, A. M. (2014). Improvements in hand function after intensive bimanual training are not associated with corticospinal tract dysgenesis in children with unilateral cerebral palsy. *Experimental Brain Research*, *232*(6), 2001–2009. https://doi.org/10.1007/s00221-014-3889-x

Garyfallidis, E., Brett, M., Amirbekian, B., Rokem, A., van der Walt, S., Descoteaux, M., Nimmo-Smith, I., & Dipy Contributors. (2014). Dipy, a library for the analysis of diffusion MRI data. *Frontiers in Neuroinformatics*, *8*, 8. https://doi.org/10.3389/fninf.2014.00008

Glenn, O. A., Ludeman, N. A., Berman, J. I., Wu, Y. W., Lu, Y., Bartha, A. I., Vigneron, D. B., Chung, S. W., Ferriero, D. M., Barkovich, A. J., & Henry, R. G. (2007). Diffusion tensor MR imaging tractography of the pyramidal tracts correlates with clinical motor function in children with congenital hemiparesis. *AJNR. American Journal of Neuroradiology*, *28*(9), 1796–1802. https://doi.org/10.3174/ajnr.A0676

Gordon, A. M., Bleyenheuft, Y., & Steenbergen, B. (2013). Pathophysiology of impaired hand function in children with unilateral cerebral palsy. *Developmental Medicine and Child Neurology*, *55 Suppl 4*, 32–37. https://doi.org/10.1111/dmcn.12304

Gordon, A. M., Hung, Y.-C., Brandao, M., Ferre, C. L., Kuo, H.-C., Friel, K., Petra, E., Chinnan, A., & Charles, J. R. (2011). Bimanual training and constraint-induced movement therapy in children with hemiplegic cerebral palsy: a randomized trial. *Neurorehabilitation and Neural Repair*, *25*(8), 692–702. https://doi.org/10.1177/1545968311402508

Gupta, D., Barachant, A., Gordon, A. M., Ferre, C., Kuo, H.-C., Carmel, J. B., & Friel, K. M. (2017). Effect of sensory and motor connectivity on hand function in pediatric hemiplegia. *Annals of Neurology*, *82*(5), 766–780. https://doi.org/10.1002/ana.25080

Holmefur, M., Kits, A., Bergström, J., Krumlinde-Sundholm, L., Flodmark, O., Forssberg, H., & Eliasson, A.-C. (2013). Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy. *Neurorehabilitation and Neural Repair*, *27*(1), 72–78. https://doi.org/10.1177/1545968312446950

Holmefur, M., Krumlinde-Sundholm, L., & Eliasson, A.-C. (n.d.). Interrater and intrarater reliability of the Assisting Hand Assessment. *The American Journal of Occupational Therapy : Official Publication of the American Occupational Therapy Association*, *61*(1), 79–84. https://doi.org/10.5014/ajot.61.1.79

Holmström, L., Lennartsson, F., Eliasson, A.-C., Flodmark, O., Clark, C., Tedroff, K., Forssberg, H., & Vollmer, B. (2011). Diffusion MRI in corticofugal fibers correlates with hand function in unilateral cerebral palsy. *Neurology*, *77*(8), 775–783. https://doi.org/10.1212/WNL.0b013e31822b0040

Holmström, L., Vollmer, B., Tedroff, K., Islam, M., Persson, J. K. E., Kits, A., Forssberg, H., & Eliasson, A.-C. (2010). Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Developmental Medicine and Child Neurology*, *52*(2), 145–152. https://doi.org/10.1111/j.1469-8749.2009.03496.x

Hung, Y.-C., Robert, M. T., Friel, K. M., & Gordon, A. M. (2019). Relationship Between Integrity of the Corpus Callosum and Bimanual Coordination in Children With Unilateral Spastic Cerebral Palsy. *Frontiers in Human Neuroscience*, *13*, 334. https://doi.org/10.3389/fnhum.2019.00334

Jaspers, E., Byblow, W. D., Feys, H., & Wenderoth, N. (2015). The Corticospinal Tract: A Biomarker to Categorize Upper Limb Functional Potential in Unilateral Cerebral Palsy. *Frontiers in Pediatrics*, *3*, 112. https://doi.org/10.3389/fped.2015.00112

Jebsen, R. H., Taylor, N., Trieschmann, R. B., Trotter, M. J., & Howard, L. A. (1969). An objective and standardized test of hand function. *Archives of Physical Medicine and Rehabilitation*, *50*(6), 311–319.

Krumlinde-Sundholm, L., & Eliasson, A.-C. (2002). Comparing tests of tactile sensibility: aspects relevant to testing children with spastic hemiplegia. *Developmental Medicine and Child Neurology*, *44*(9), 604–612. https://doi.org/10.1017/s001216220100264x

Krumlinde-Sundholm, L., Holmefur, M., Kottorp, A., & Eliasson, A.-C. (2007). The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change. *Developmental Medicine and Child Neurology*, *49*(4), 259–264. https://doi.org/10.1111/j.1469-8749.2007.00259.x

Kuczynski, A. M., Carlson, H. L., Lebel, C., Hodge, J. A., Dukelow, S. P., Semrau, J. A., & Kirton, A. (2017). Sensory tractography and robot-quantified proprioception in hemiparetic children with perinatal stroke. *Human Brain Mapping*, *38*(5), 2424–2440. https://doi.org/10.1002/hbm.23530

Kuczynski, A. M., Dukelow, S. P., Hodge, J. A., Carlson, H. L., Lebel, C., Semrau, J. A., & Kirton, A. (2018). Corticospinal tract diffusion properties and robotic visually guided reaching in children with hemiparetic cerebral palsy. *Human Brain Mapping*, *39*(3), 1130–1144. https://doi.org/10.1002/hbm.23904

Kuczynski, A. M., Kirton, A., Semrau, J. A., & Dukelow, S. P. (2018). Bilateral reaching deficits after unilateral perinatal ischemic stroke: a population-based case-control study. *Journal of NeuroEngineering and Rehabilitation*, *15*(1), 77. https://doi.org/10.1186/s12984-018-0420-9

Law, M., Baptiste, S., McColl, M., Opzoomer, A., Polatajko, H., & Pollock, N. (1990). The Canadian occupational performance measure: an outcome measure for occupational therapy. *Canadian Journal of Occupational Therapy. Revue Canadienne d'ergotherapie*, *57*(2), 82–87. https://doi.org/10.1177/000841749005700207

Mackey, A., Stinear, C., Stott, S., & Byblow, W. D. (2014). Upper limb function and cortical organization in youth with unilateral cerebral palsy. *Frontiers in Neurology*, *5*, 117. https://doi.org/10.3389/fneur.2014.00117

Marneweck, M., Kuo, H.-C., Smorenburg, A. R. P., Ferre, C. L., Flamand, V. H., Gupta, D., Carmel, J. B., Bleyenheuft, Y., Gordon, A. M., & Friel, K. M. (2018). The Relationship Between Hand Function and Overlapping Motor Representations of the Hands in the

Contralesional Hemisphere in Unilateral Spastic Cerebral Palsy. *Neurorehabilitation and Neural Repair*, *32*(1), 62–72. https://doi.org/10.1177/1545968317745991

McNeish, D. M., & Stapleton, L. M. (2016). The Effect of Small Sample Size on Two-Level Model Estimates: A Review and Illustration. *Educational Psychology Review*, *28*(2), 295–314. https://doi.org/10.1007/s10648-014-9287-x

Mori, S., Crain, B. J., Chacko, V. P., & van Zijl, P. C. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, *45*(2), 265–269. https://doi.org/10.1002/1531-8249(199902)45:2<265::aid-ana21>3.0.co;2-3

Mulcahey, M. J., Kozin, S., Merenda, L., Gaughan, J., Tian, F., Gogola, G., James, M. A., & Ni, P. (2012). Evaluation of the box and blocks test, stereognosis and item banks of activity and upper extremity function in youths with brachial plexus birth palsy. *Journal of Pediatric Orthopedics*, *32 Suppl 2*, S114-22. https://doi.org/10.1097/BPO.0b013e3182595423

Nemanich, S. T., Mueller, B. A., & Gillick, B. T. (2019). Neurite orientation dispersion and density imaging quantifies corticospinal tract microstructural organization in children with unilateral cerebral palsy. *Human Brain Mapping*, *40*(17), 4888–4900. https://doi.org/10.1002/hbm.24744

Novak, I., McIntyre, S., Morgan, C., Campbell, L., Dark, L., Morton, N., Stumbles, E., Wilson, S.-A., & Goldsmith, S. (2013). A systematic review of interventions for children with cerebral palsy: state of the evidence. *Developmental Medicine and Child Neurology*, *55*(10), 885–910. https://doi.org/10.1111/dmcn.12246

O'Connor, B., Kerr, C., Shields, N., & Imms, C. (2016). A systematic review of evidence-based assessment practices by allied health practitioners for children with cerebral palsy. *Developmental Medicine and Child Neurology*, *58*(4), 332–347. https://doi.org/10.1111/dmcn.12973

Oskoui, M., Coutinho, F., Dykeman, J., Jetté, N., & Pringsheim, T. (2013). An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Developmental Medicine and Child Neurology*, *55*(6), 509–519. https://doi.org/10.1111/dmcn.12080

Peters, C., Chang, A., Morales, A., Barnes, K., & Allegretti, A. (2019). An integrative review of assessments used in occupational therapy interventions for children with cerebral palsy. *Cadernos Brasileiros de Terapia Ocupacional*, *27*(1), 168–185. https://doi.org/10.4322/2526-8910.ctoAR1856

Platz, T., Pinkowski, C., van Wijck, F., Kim, I.-H., di Bella, P., & Johnson, G. (2005). Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clinical Rehabilitation*, *19*(4), 404–411. https://doi.org/10.1191/0269215505cr832oa

R Lowrey, C. (2014). A Novel Robotic Task for Assessing Impairments in Bimanual Coordination Post-Stroke. *International Journal of Physical Medicine & Rehabilitation*, *s3*(01). https://doi.org/10.4172/2329-9096.S3-002

Riquelme, I., Arnould, C., Hatem, S. M., & Bleyenheuft, Y. (2019). The Two-Arm Coordination Test: Maturation of Bimanual Coordination in Typically Developing Children and Deficits in Children with Unilateral Cerebral Palsy. *Developmental Neurorehabilitation*, *22*(5), 312–320. https://doi.org/10.1080/17518423.2018.1498552

Robert, M. T., Gutterman, J., Ferre, C. L., Chin, K., Brandao, M. B., Gordon, A. M., & Friel, K. (2021). Corpus Callosum Integrity Relates to Improvement of Upper-Extremity Function Following Intensive Rehabilitation in Children With Unilateral Spastic Cerebral Palsy. *Neurorehabilitation and Neural Repair*, *35*(6), 534–544. https://doi.org/10.1177/15459683211011220

Rocca, M. A., Turconi, A. C., Strazzer, S., Absinta, M., Valsasina, P., Beretta, E., Copetti, M., Cazzagon, M., Falini, A., & Filippi, M. (2013). MRI predicts efficacy of constraint-induced movement therapy in children with brain injury. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics*, *10*(3), 511–519. https://doi.org/10.1007/s13311-013-0189-2

Rosenbaum, P., Paneth, N., Leviton, A., Goldstein, M., Bax, M., Damiano, D., Dan, B., & Jacobsson, B. (2007). A report: the definition and classification of cerebral palsy April 2006. *Developmental Medicine and Child Neurology. Supplement*, *109*, 8–14.

Shierk, A., Lake, A., & Haas, T. (2016). Review of Therapeutic Interventions for the Upper Limb Classified by Manual Ability in Children with Cerebral Palsy. *Seminars in Plastic Surgery*, *30*(1), 14–23. https://doi.org/10.1055/s-0035-1571256

Sköld, A., Hermansson, L. N., Krumlinde-Sundholm, L., & Eliasson, A.-C. (2011). Development and evidence of validity for the Children’s Hand-use Experience Questionnaire (CHEQ). *Developmental Medicine and Child Neurology*, *53*(5), 436–442. https://doi.org/10.1111/j.1469-8749.2010.03896.x

Smorenburg, A. R. P., Gordon, A. M., Kuo, H.-C., Ferre, C. L., Brandao, M., Bleyenheuft, Y., Carmel, J. B., & Friel, K. M. (2017). Does Corticospinal Tract Connectivity Influence the Response to Intensive Bimanual Therapy in Children With Unilateral Cerebral Palsy? *Neurorehabilitation and Neural Repair*, *31*(3), 250–260. https://doi.org/10.1177/1545968316675427

Staudt, M. (2002). Two types of ipsilateral reorganization in congenital hemiparesis: A TMS and fMRI study. *Brain*, *125*(10), 2222–2237. https://doi.org/10.1093/brain/awf227

Staudt, M., Gerloff, C., Grodd, W., Holthausen, H., Niemann, G., & Krägeloh-Mann, I. (2004). Reorganization in congenital hemiparesis acquired at different gestational ages. *Annals of Neurology*, *56*(6), 854–863. https://doi.org/10.1002/ana.20297

Taub, E., Uswatte, G., Mark, V. W., & Morris, D. M. M. (2006). The learned nonuse phenomenon: implications for rehabilitation. *Europa Medicophysica*, *42*(3), 241–256.

Taylor, N., Sand, P. L., & Jebsen, R. H. (1973). Evaluation of hand function in children. *Archives of Physical Medicine and Rehabilitation*, *54*(3), 129–135.

Theaud, G., Houde, J.-C., Boré, A., Rheault, F., Morency, F., & Descoteaux, M. (2020). TractoFlow: A robust, efficient and reproducible diffusion MRI pipeline leveraging Nextflow & Singularity. *NeuroImage*, *218*, 116889. https://doi.org/10.1016/j.neuroimage.2020.116889

Tsai, L., Lin, K., Liao, H., & Hsieh, C. (2009). Reliability of two visual-perceptual tests for children with cerebral palsy. *The American Journal of Occupational Therapy : Official Publication of the American Occupational Therapy Association*, *63*(4), 473–480. https://doi.org/10.5014/ajot.63.4.473

Tyryshkin, K., Coderre, A. M., Glasgow, J. I., Herter, T. M., Bagg, S. D., Dukelow, S. P., & Scott, S. H. (2014). A robotic object hitting task to quantify sensorimotor impairments in participants with stroke. *Journal of Neuroengineering and Rehabilitation*, *11*, 47. https://doi.org/10.1186/1743-0003-11-47

van der Aa, N. E., Verhage, C. H., Groenendaal, F., Vermeulen, R. J., de Bode, S., van Nieuwenhuizen, O., & de Vries, L. S. (2013). Neonatal neuroimaging predicts recruitment of contralesional corticospinal tracts following perinatal brain injury. *Developmental Medicine and Child Neurology*, *55*(8), 707–712. https://doi.org/10.1111/dmcn.12160

Verkerk, G. J. Q., Wolf, M. J. M. A. G., Louwers, A. M., Meester-Delver, A., & Nollet, F. (2006). The reproducibility and validity of the Canadian Occupational Performance Measure in parents of children with disabilities. *Clinical Rehabilitation*, *20*(11), 980–988. https://doi.org/10.1177/0269215506070703

Waddell, K. J., & Lang, C. E. (2018). Comparison of Self-Report Versus Sensor-Based Methods for Measuring the Amount of Upper Limb Activity Outside the Clinic. *Archives of Physical Medicine and Rehabilitation*, *99*(9), 1913–1916. https://doi.org/10.1016/j.apmr.2017.12.025

Zielinski, I. M., Jongsma, M. L. A., Baas, C. M., Aarts, P. B. M., & Steenbergen, B. (2014). Unravelling developmental disregard in children with unilateral cerebral palsy by measuring event-related potentials during a simple and complex task. *BMC Neurology*, *14*, 6. https://doi.org/10.1186/1471-2377-14-6