MULTIMODAL MAPPING OF BRAIN–BEHAVIOR RELATIONSHIPS IN CEREBRAL PALSY: LINKING ROBOTIC UPPER LIMB ASSESSMENT WITH MOBILE FUNCTIONAL NEUROIMAGING

by

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(Under the Direction of Christopher M Modlesky)

ABSTRACT

The purpose of this dissertation was to examine the influence of motor control impairments and aberrant prefrontal cortex (PFC) activity on upper limb dysfunction in children with cerebral palsy (CP) during goal-directed actions. A multimodal framework combined robotic assessments with mobile functional neuroimaging using functional near-infrared spectroscopy (fNIRS) to investigate brain–behavior relationships during naturalistic, time-constrained reaching and interception tasks. The first aim was to determine whether children with CP displayed impaired motor performance and planning during stationary target reaching and moving target interception, and to assess if deficits varied across time constraints. Children with CP exhibited task- and limb-specific impairments in reaching accuracy, trajectory planning, and response preparedness, with deficits more pronounced in the non-preferred arm and under stricter time restrictions. The second aim was to assess relationships between robotic metrics and established clinical measures of manual ability. Results indicated robotic metrics recorded under high time pressure were directly and moderately related to manual ability in children with CP. The

third aim was to determine PFC activity during time-constrained reaching and assess its relationship to reaching accuracy. An atypical pattern of suppressed PFC activity was observed in CP, with increased PFC recruitment moderate-strongly related to improved motor accuracy, with relationships more pronounced across temporal constraints for the ipsilateral PFC. The fourth aim was to determine PFC activity patterns during time-constrained interception, and to assess their relationship to robotic metrics of interception planning and performance. Children with CP exhibited atypical patterns of suppressed contralateral PFC activity and ipsilateral PFC dominance with the non-preferred arm, with greater contralateral activity and higher ipsilateral dominance both related to faster responses in this group.

These findings provide compelling evidence that children with CP exhibit persistent, limb-specific, and context-dependent impairments in motor planning and execution, that are influenced by altered cortical activation patterns. Robotic metrics sensitively reflect functional capacity, while PFC activity offers a potential biomarker for adaptive versus maladaptive compensatory strategies. These results lay the empirical groundwork for the development of individualized interventions that are informed by personalized profiles of motor behavior and brain function.

INDEX WORDS: Cerebral palsy, prefrontal cortex, reaching, interception, neuroimaging, functional near infrared spectroscopy, lateralization, neuroplasticity, motor control

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DEDICATION

This dissertation is dedicated to the children with cerebral palsy and their families, whose time, trust, and faith in our efforts drive this work.

Your strength of spirit and resilience are a source of constant inspiration. Thank you for the privilege of the opportunity to work with, and for you.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1. Background

Cerebral palsy (CP) is an umbrella term that describes a group of neurodevelopmental disorders of posture and movement arising from non-progressive damage to the developing brain (1, 2). As the commonest cause of childhood-onset movement disability, CP affects 1 in 323 children in the United States. The economic impact of CP-related morbidity is significant, with estimated lifetime expenditure of $921,000 per individual with CP (3) contributing to the estimated lifetime costs of more than $10 billion associated with CP (4). Up to 60% of children with CP show impaired arm and hand use (5) which hampers the independent performance of daily tasks (6) and limits participation in functional peer-play, leisure activities and sports (7). The rapid and continual multi-system integration required to perform goal-directed arm movements is especially challenging for children with CP, who show marked central deficits in motor planning (8) visuospatial attention (9) and visuomotor coordination (10), in addition to their sensorimotor impairments. Clinical assessments of upper limb function in CP demonstrate low objectivity, questionable reliability and inconsistent responsiveness to meaningful clinical change following interventions (11). Additionally, these timed, behavioral evaluations provide unidimensional information of arm and hand use that does not account for the complex, multifactorial nature of upper limb dysfunction in CP.

Recent advancements in robotic technologies have provided a reliable (12) and objective means to interrogate sensorimotor (13-20), visuoperceptual (21) and cognitive deficits (22, 23) in children with CP, with recent reports extending its feasibility to adults with CP (24, 25). Key

advantages of robotic technologies over conventional clinical evaluations include (a) greater objectivity via reduced assessor bias, (b) enhanced precision and sensitivity of quantitative metrics compared to ordinal or dichotomous scales, and (c) improved user engagement and compliance through novel and interactive game-based assessment approaches. Building on previous research using motion capture during reaching movements (6, 26), robotic analyses revealed that children with arterial stroke-induced CP display global impairments during reaching tasks, which are linked to established clinical measures of manual ability (14). Importantly, standardized robotic tasks can be combined with neurophysiological assessments to provide insights into brain-behavior relationships following early brain injury. For example, sensory deficits identified through robotic reaching assessments were linked to aberrant sensory tract development in children with perinatal stroke (15), highlighting how multimodal integration of robotic tools and neuroimaging can enhance understanding of motor impairments in CP.

Moving-target interception represents a complex motor challenge that is integral to functional independence, requiring individuals to continuously process multisensory inputs, allocate attention, and generate coordinated and timely motor responses towards a predicted target position (27-29). The dynamic interplay of anticipatory (feedforward) motor planning and real-time feedback adjustments required for successful interception (30) renders it suitable to probe goal-directed actions in individuals with neurological damage (31). In CP, disruptions in sensory feedback processes delay response execution (32), forcing greater reliance on predictive mechanisms to compensate for slower online corrections (30). These deficits, coupled with impairments in spatial attention (9) and motion perception (33), significantly reduce the accuracy of movement adjustments during dynamic tasks. Moreover, central deficits in action planning are persistent across development (34) and further limit motor function (35, 36). However, interception tasks provide continuous visual input and externally imposed timing constraints which may scaffold movement planning and sensorimotor coordination in CP through recruitment of more automatic visuomotor pathways and sensory-perceptual networks. In contrast, stationary reaching

is reliant on internally generated timing and movement planning, which may expose or amplify anticipatory control deficits in this group. These differences suggest that time-constrained reaching to stationary targets may evoke greater performance deficits than corresponding tasks involving moving target interception, though direct empirical comparisons across these contexts remain limited. Additionally, despite the real-world significance of these impairments, the cortical mechanisms underlying interception in CP remain largely unexamined, underscoring the need for targeted research utilizing robotic assessments combined with functional neuroimaging.

While robotic technologies have seen rapid technical advances, the translation of robot-derived metrics into actionable insights that can inform therapeutic strategies requires a deeper understanding of neurophysiological mechanisms at play in CP. Conventional neuroimaging modalities such as functional magnetic resonance imaging and magnetoencephalography are unable to capture real-time neural activity during dynamic, goal-directed movements in natural environments, and are particularly challenging for children with CP who commonly struggle with attentional demands and movement restrictions. Conversely, electroencephalography offers free mobility, but lacks the spatial resolution to adequately localize brain activity (37). Functional near-infrared spectroscopy (fNIRS) is a non-invasive, motion-tolerant, and portable optical neuroimaging tool (38) that can silently capture cortical activity during real-world tasks (39), making it particularly well-suited for children with CP (40). Most fNIRS studies in CP has investigated cortical activity and functional connectivity within the sensorimotor cortices during simple single joint/limb movements (41-49), revealing exaggerated cortical activity linked to impaired selective motor control (42) and widespread muscle activation (45, 47, 48). In contrast, surprisingly few studies have explored the role and impact of prefrontal cortex (PFC) during movement, reflecting the lack of neurophysiological insight into aberrant cognitive-motor interactions following neural insults (50).

The PFC is a critical node in the frontoparietal network for goal-directed reaching, where it plays a key role in action planning (51), prediction (52), and priming the sensorimotor cortices

for expected sensory input (53). It is also a cortical hub for visuospatial attention and spatial localization (54), functions that are essential for accurate, targeted reaching. While PFC activity has been examined in neurotypical adults during reaching (55), its role in CP has primarily been studied in the context of motor planning (56) and cognitive-motor dual-tasks (57-59). Interestingly, children with CP exhibit heightened PFC activity during these tasks, potentially reflecting neural resource reallocation to compensate for postural and balance deficits. Additionally, PFC activity has been shown to normalize following intensive intervention (59), suggesting it may serve as a marker for neuroplasticity. However, despite these initial findings, no study has yet determined PFC activity during goal-directed reaching in children with CP.

1.2. Dissertation Aims and Hypotheses

Below are the dissertation aims and associated hypotheses:

Specific aim 1: To map and critically appraise the literature on the feasibility and current use of functional near-infrared spectroscopy (fNIRS) to assess cortical activity, functional connectivity, and neuroplasticity in individuals with cerebral palsy (CP).

Specific aim 2: To determine if children with CP exhibit deficits in motor performance and planning during stationary target reaching and moving target interception, and if the expected performance deficits vary across imposed time constraints.

Hypothesis 2.1: Children with CP will exhibit lower motor performance (i.e., lower accuracy, larger spatial errors, slower peak velocities) and motor planning deficits (i.e., slower reaction time, lower initial movement angles) than matched controls during both tasks.

Hypothesis 2.2: Performance deficits will be greater during stationary target reaching and under high time constraints.

Hypothesis 2.3: Planning deficits will be similar across both tasks and all time constraints.

Specific aim 3: To determine the relationship between robotic metrics and clinical assessments of manual ability in children with CP.

Hypothesis 3.1: Better robotic metrics of motor performance and planning will be related to higher clinical assessment scores in children with CP.

Specific aim 4: To determine PFC activity during time-constrained reaching of stationary targets in children with CP, and to determine the relationship between PFC activity and reaching accuracy.

Hypothesis 4.1: Children with CP will display greater PFC activity and worse reaching performance during time-constrained reaching than matched controls.

Hypothesis 4.2: Greater PFC activity will be related to higher reaching accuracy in children with CP.

Specific aim 5: To determine prefrontal cortex activity during time-constrained interception of moving targets in children with CP, and to determine the relationship between PFC activity and interception performance and planning metrics.

Hypothesis 5.1: Children with CP will display lower and more lateralized PFC activity, and worse motor performance and planning during time-constrained interception than matched controls.

Hypothesis 5.2: Greater PFC activity will be related to better interception performance and planning metrics in children with CP.

1.3 Innovation and Significance

This dissertation pioneers the concurrent use of mobile functional neuroimaging with robotic assessments to investigate brain-behavior relationships underlying upper limb dysfunction in children with CP. By leveraging the sensitivity and precision of robotic kinematics with the high spatiotemporal resolution and motion tolerance of fNIRS, this work simultaneously captures motor

performance and neurophysiological dynamics during naturalistic behaviors such as goal-directed reaching and moving target interception. This multimodal approach enables real-time assessment of how PFC engagement influences motor planning, execution, and adaptability across varying task constraints—an area previously underexplored in pediatric neurorehabilitation research.

Importantly, this integrative framework differs from conventional assessment approaches that evaluate neural and behavioral components in isolation. Instead, it grounds motor dysfunction in cognitive-motor theories by characterizing PFC involvement in movement prediction, planning, and resource allocation during upper limb actions. This work systematically investigates these dynamics across task types, time constraints, and arm dominance, with an aim to delineate both compensatory and maladaptive neural strategies used by children with CP.

By linking highly granular robotic metrics with standardized clinical assessments, and uncovering cortical markers of motor impairment, this dissertation lays the empirical groundwork for developing neurophysiology-informed therapies to support the individual rehabilitation needs of children with CP. As fNIRS technologies continue to evolve with scalable, high-density optode arrays alongside improved spatial resolution and enhanced motion tolerance, the findings from this dissertation may help promote more targeted neurorehabilitation strategies based on personalized brain-behavior dynamics in individuals with early brain injury.

1.4. Literature review: Cerebral palsy (CP)

1.4.1. Definition, etiology, and epidemiology of CP

Cerebral palsy is an umbrella term (1) that describes a group of neurodevelopmental permanent disorders of movement and posture that cause activity limitations and arise from non-progressive damage of the developing brain (60). First described in the 1827 medical thesis of French neurologist Jean-Baptiste Cazauvieilh (61), the terminology used to describe this condition has undergone several revisions (62, 63), and continues to be a topic of active debate (64-67). Underlying this complexity of terminology is the multifactorial and diverse etiology of CP (68).

Preterm birth is the strongest risk factor for CP (69, 70), with additional pre-, peri-, and early post-natal risk factors including maternal infections, inflammation, intrauterine growth retardation and birth asphyxia (71) potentially having an additive effect for CP risk (72). The strong links between low socioeconomic status, low birth weight and risk of preterm births may also underlie the disproportionately greater prevalence of CP reported in Black individuals in the United States (73), and may also contribute to the greater prevalence rates reported in low- and middle-income developing countries (74, 75). The most recent estimates report CP prevalence in high-income countries at 1.5-1.6 per 1000 live births (75), cementing its status as the most common cause of childhood-onset motor disability. This high prevalence is compounded by lifetime healthcare costs exceeding a million USD per individual with CP (3), with the total CP-related burden on the US economy exceeding 10 billion USD per year (4).

The etiological complexity of CP is also reflected in the heterogeneous pathophysiological mechanisms. These include early brain injury and/or maldevelopment due to one or more of the abovementioned causes, with genetic susceptibility in the form of single-gene mutations and copy number variations being increasing recognized as important predisposing risk factors (71, 76). The pathologies seen in CP vary by time of injury: Periventricular leukomalacia (PVL) is most frequently observed in preterm infants (77), hypoxic-ischemic encephalopathy is more common at or immediately following labor (78), while neonatal and perinatal strokes occur between 20 weeks of gestation to 28 days after birth (79, 80).

The extent and location of brain damage determine the clinical manifestations, severity of motor impairments, and associated comorbidities. Primarily white matter lesions like PVL are characterized by damage to the metabolically active sensorimotor tracts encasing the third ventricle, and are driven by disrupted autoregulation of the developmentally immature cerebral vasculature in the preterm infant (81). The bilateral topological arrangement of descending motor fibers (corticospinal tract, CST) predisposes both lower extremities to greater injury, most often resulting in a spastic diplegic presentation with greater lower limb involvement, though upper limb dystonia

is frequently observed (82) and is linked to functional disability in this group (83). Similar PVL damage also accounts for nearly half (45%) of children with unilateral CP (84). Conversely, perinatal strokes are more commonly observed in term infants and have distinct pathophysiologic mechanisms (85), appearing as focal injuries within the first week of life (86) that underlie up to 30% of cases of spastic hemiplegic CP (84). While 5 distinct perinatal stroke syndromes have been described (87) that show distinct functional outcomes (88), neonatal arterial lesions of the major cerebral vessels, most commonly the left middle cerebral artery (89), appear to underlie the disproportionately greater upper extremity involvement observed in hemiplegic CP. However, up to 15% of infants with CP display no neuroradiological abnormality (90-92), and heightened neuroplasticity in early life (i.e., the Kennard principle (93, 94)) can help compensate for loss of neuronal function (95-98), which cautions against deriving simplistic structure-function relationships in this clinically heterogenous group.

1.4.2. Clinical features of CP

Clinical manifestations of CP are diverse, and include impairments in neuromotor, sensory-perceptual, cognitive, and communicative functions. Neuromotor impairments are most prominent, with disordered posture and movement forming a key diagnostic criterion for CP. These are conventionally grouped into positive and negative clinical signs (99). Positive clinical features represent unintentional, excessive motor activation or movement patterns, and are characterized by hypertonia, hyperreflexia, or tremors (99). The most prominent of these is hypertonia, with its commonest form being spasticity (70-80% of CP cases), defined as the velocity-dependence increase in responsiveness to the tonic-stretch reflex (100, 101). Despite the visual prominence of spasticity which made it a primary therapeutic target in early rehabilitative efforts, spasticity remains poorly defined (102) and explains a significantly smaller variance in functional abilities in CP than muscle weakness (103). Other forms of hypertonia include dystonia, which refers to involuntary sustained or intermittent contractions causing repetitive or twisting movements alone,

or in conjunction with, abnormal postures (104). In conjunction with the infrequent choreoathetoid forms that involve involuntary writhing movements, these symptoms typically arise from damage to the basal nuclei and together constitute dyskinetic CP (105) (10-15% of CP cases). Negative signs describe inadequate activation or control of muscles, and include clinical features such as muscle weakness, poor selective motor control, and dyscoordination (106) that are harder to clinically observe and quantify, but significantly contribute to functional disabilities in CP (103, 107-110). Ataxic CP, the rarest subtype comprising 5% of CP cases, typically manifests as postural instability, vestibular dysfunction, and balance disorders following damage to the pontine-cerebellar regions (76).

Beyond motor manifestations, individuals with CP commonly report sensory-perceptual deficits (25), with impairments in proprioceptive (18), tactile-discriminative (111), visuomotor (10), and visuoperceptual (112) functions acting as barriers to function independence and participation (113). Notably, sensory deficits may directly impact motor function in CP; Hoon et al. (114) reported damage to ascending sensory pathways (thalamo-cortical tracts) following PVL in individuals with spastic diplegia significantly impacted sensory functions, strength, and ambulatory capacity (114), highlighting the contribution of sensory systems to motor production in this group. Visuoperceptual deficits such as impaired spatial attention and poor motion perception (33) further disrupt sensorimotor coordination. Additionally, over half of individuals with CP display some form of cognitive impairment (115), with action planning deficits hindering effective motor learning (35) and contributing to maladaptive compensatory strategies such as over-reliance on vision for movement execution (10). This combination of motor, sensory, perceptual and cognitive impairments significantly influences the functional independence and quality of life of individuals with CP.

1.5. Literature review: Upper limb dysfunction in CP

1.5.1. Clinical manifestations of upper limb dysfunction in CP

Upper extremity dysfunction is a significant concern for individuals with CP, affecting daily activities (116), functional independence in self-care (117, 118), and participation in social and recreational activities (119). Arm and hand use difficulties are highly prevalent in CP, with more than minor difficulties with hand use reported by up to 60% of individuals in a population-based CP study (5) and 83% of children with CP attending a non-hand CP clinic (120). These deficits arise from the complex interaction of motor, sensory, and cognitive impairments, resulting in difficulties with goal-directed reaching (121), grasping, and object manipulation during self-care tasks like eating, dressing, and writing (11). Diminished dexterity hinders academic performance, affecting writing, drawing, and keyboard use (122), which can lead to reduced independence and self-efficacy. This adversely impacts the child's ability to engage in and persist with challenging tasks (123), which negatively influences therapeutic outcomes in the long-term (124, 125).

Tasks requiring bimanual control (e.g., buttoning, handling cutlery, tying shoelaces) are especially challenging for individuals with poor selective motor control (126) and bimanual dyscoordination (127, 128). The latter arises from asymmetrical CST connectivity (detailed in section below) and interrupted inter-hemispheric communication pathways (129, 130); this is especially problematic in unilateral CP, where CST damage prevents the establishment of contralateral cortical control of the affected limb (131) and results in persistent weakness and underuse ("learned non-use" (132)) of the paretic hand. This developmental disregard further exacerbates functional limitations, as children preferentially rely on their less impaired hand for daily despite evidence of preserved capacity in the more affected arm (133), ostensibly to minimize the cognitive-attentional demands associated with movements in the latter. Support for this aberrant cognitive-motor interaction comes from functional neuroimaging studies (58, 134) revealing that children with unilateral CP exhibit increased cognitive load (134) and greater activation of the

prefrontal cortex (PFC) during upper limb dual-tasks (58), likely reflecting compensatory recruitment of cognitive resources to support motor execution (57, 135).

1.5.2. Neural bases of upper limb dysfunction in CP

The extent and nature of upper limb dysfunction depends on the severity, location, and extent of brain injury (136). As upper limb impairments are most commonly observed in unilateral spastic CP (120), and due to their constrained unilateral brain lesions (98), most research on pathophysiological mechanisms has been limited to this group (137). Of specific importance to manual ability is the corticospinal tract (CST), which mediates fine control and dexterous function in humans as well as other mammals . During typical early development (~20th week of gestation), CST projections arising from the motor cortices form synaptic connections with target alpha motor neurons at the spinal segmental level that supply both ipsilateral and contralateral upper extremity musculature (138). Ipsilateral CST projections are gradually weakened ("withdrawn" (139)) by competitive inhibition that is driven mainly by primary motor cortex activity during development, resulting in the predominant contralateral CST control seen in neurotypical adults (140). These CST projections form direct connections with motor neurons innervating hand musculature, making the CST essential for selective finger control and individuation abilities that underlie dexterity and fine motor skills (141).

Brain damage during the perinatal period can adversely alter these delicate developmental processes (131). Three major patterns of CST rewiring have been described (142), with CST development dependent on the timing, extent, and type of injury (142). Specifically, injuries or malformation during early development (conception-24 weeks) generally produces less severe hand dysfunction compared to PVL (24-34 weeks) or perinatal stroke during the late 3rd trimester (140), though this is debated (84). Unilateral injury can partly or completely terminate contralateral CST connections, with the resultant attenuation of synaptic competition allowing ipsilateral CST fibers to be preserved and/or strengthened. Small-moderate lesions may allow some contralateral

CST projections to be spared, with the added potential for compensatory activation of ipsilateral supplementary motor areas, allowing for better hand function (143). Perinatal strokes and lesions in the late third trimester (34-38 weeks) commonly impact cortical-subcortical grey matter and parasagittal tissues and rarely extend medially to affect periventricular white matter, with at least partial sparing of contralateral fibers allowing for bilateral CST control. Conversely, larger periventricular lesions (144) and those occurring before 34 weeks of gestation may fully abolish contralateral CST projections, with the ipsilateral CST strengthening over time (139) to take over sole or major control of motor function in the affected upper extremity (145).

Notably, sensory pathways do not appear to follow this reorganization pattern (145), with afferent thalamo-cortical fibers commonly 'bypassing' even large lesion sites to connect to the affected contralateral cortex (146, 147). This may occur due to prominent developmental differences in thalamo-cortical growth in preterm compared to at-term newborns (148). Afferent projections in the preterm are still growing and tend to 'wait' at subcortical layers till late in the third trimester, with increased vulnerability from rapid axonal growth in periventricular regions countered by high synaptogenesis and neuroplastic potential in the event of injury (e.g., PVL (114)). Conversely, at-term newborns experience significant intra-cortical organization of afferent projections with sensory experiences in early life, and are thus more vulnerable to sensory loss from cortical injuries (148), a claim backed by empirical evidence (149).

The severity of upper extremity clinical manifestations is also dependent on the type and location of brain injury. In children with unilateral CP, greater deficits in manual ability and hand function were observed with cortical-subcortical grey matter lesions compared to white matter lesions like PVL (150), though large individual variability in functional outcomes were observed within each group (151). Lesion size also impacts function in this group, with larger grey matter lesions explaining greater variance (65-75%) in manual ability than white matter damage extent and location (12-24%) (150). Damage to deep grey matter structures like the basal nuclei and thalamus are consistently linked to poor upper limb function (151-154). Preserved sensorimotor

thalamic connections is reported to have a greater impact on paretic hand function than CST fibers in children with PVL-induced hemiplegic CP (155), with microstructural abnormalities of these important thalamocortical fibers also related to both sensory and motor deficits (156). Despite this growing body of evidence, significant variability in sensorimotor neurophysiology exists across individuals with CP (157), rendering efforts to delineate straight-forward structure-function relationships ineffectual.

The remarkable neuroplastic potential of the developing brain underlies the wide heterogeneity observed in motor outcomes following perinatal stroke (158). Unlike adult stroke, where focal lesions often produce predictable deficits, even large early-life lesions may result in unexpectedly mild motor impairments due to adaptive reorganization of cortical and subcortical systems (159). This developmental plasticity is supported by age-dependent mechanisms such as axonal sprouting, synaptogenesis, and recruitment of alternative motor pathways (e.g., ipsilateral CST projections, bilateral supplementary motor area involvement) that are largely absent or limited in maturity in the adult brain (97). Evidence from neuroimaging and neurophysiological studies suggests that such reorganization can preserve motor function, particularly when injury occurs during windows of heightened developmental plasticity (98, 131). However, the nature and extent of this reorganization vary across individuals (160), shaped by lesion timing, location, and genetic and environmental influences that contribute to the clinical heterogeneity (143) and differential responses to intervention that characterizes children with CP (161)

1.6. Functional neuroimaging in CP

1.6.1. Conventional neuroimaging modalities used in CP

Functional neuroimaging provides important insights into neurophysiological dynamics during task performance in CP that promotes deeper understanding of brain function, connectivity, and neuroplasticity (162, 163). Among these modalities, functional magnetic resonance imaging (fMRI) remains the most widely used technique, leveraging blood oxygen level-dependent (BOLD)

contrasts to map task-evoked neural activity (163, 164) and assess functional connectivity at rest (165). Technical advances have seen fMRI used for investigating adaptive (interventional) neuroplasticity following rehabilitation (166) and characterizing functional connectivity patterns (167). Despite its high spatial resolution, fMRI's reliance on hemodynamic responses limits its temporal resolution and introduces susceptibility to motion artifacts (but see (168)), posing challenges in pediatric CP populations (169, 170).

To overcome these limitations, imaging techniques that can directly assess neuronal activity with high temporal resolution, such as electroencephalography (EEG) and magnetoencephalography (MEG), have been increasing used in CP. By capturing neuronal oscillations in real-time, EEG studies in CP have reported attenuated mu-band activity (171) in the ipsilesional sensorimotor cortex during upper limb tasks (157, 172, 173) and bilateral sensorimotor activation during treadmill walking (174). Studies using MEG have identified altered visual (175-177), somatosensory (178), and sensorimotor cortical dynamics (179), highlighting deficits in action planning (180). These techniques also demonstrate sensitivity to neuroplasticity-driven changes, with MEG metrics showing altered oscillatory activity following rehabilitation (181, 182).

Despite their utility, practical limitations and methodological constraints have impeded the use of these modalities in individuals with CP. Scanner-based modalities like MEG and fMRI have stringent motion control requirements, provoke scanner-induced anxiety, and exert high operational costs that restrict application in children who experience involuntary movements (e.g., dyskinetic CP (183)) and difficulty sustaining task engagement (184). Although adaptations such as child-friendly protocols and motion correction strategies have improved data quality and compliance rates (185, 186), issues related to movement artifacts, data loss, and selection bias persist, ultimately limiting the generalizability of findings (187). For example, even children with mild manual impairments struggle to comply with simple hand movement paradigms during fMRI tasks (157), leading to significant challenges in studying motor function across different CP subtypes. These barriers underscore an urgent need for child-friendly, non-invasive, and motion-tolerant functional

neuroimaging approaches that can be seamlessly integrated with ecologically valid, real-world tasks. The development of portable neuroimaging solutions holds great promise for advancing CP research, as it allows for naturalistic motor assessments without the constraints of traditional scanner-based systems.

1.6.2. Functional near-infrared spectroscopy (fNIRS) in CP

Functional near-infrared spectroscopy (fNIRS) has gained traction as a non-invasive and cost-effective alternative to conventional neuroimaging modalities, offering high motion tolerance, portability, and methodological versatility for ecologically valid real-world neuroimaging in neurodevelopmental disorders. The growing adoption of fNIRS in neurodivergent populations, including individuals with CP (188), autism spectrum disorder (189-191), pediatric TBI (192), Down's syndrome (193), and attention-deficit/hyperactivity disorder (194), underscores its utility in populations where conventional scanner-based imaging is challenging (193). Like fMRI, this technique relies on neurovascular coupling (195, 196), where increased metabolic demands of active neuronal populations provoke localized vasodilation (197). The increased blood flow results in a rise in oxyhemoglobin (HbO) and a concurrent decrease in deoxyhemoglobin (HbR) concentrations. Near-infrared light (650-900 nm optical window range (198)) emitted through fNIRS optodes placed on the scalp penetrates the underlying tissue and is attenuated via absorption, scattering, and reflection by cortical and extra-cortical tissue, before being detected by detectors on re-emerging at the scalp. The loss of light intensity can be mathematically modelled using the modified Beer-Lambert Law (199), which accounts for tissue concentrations, scattering, absorption and refraction to obtain estimates of relative changes in HbO and HbR concentrations. Together, these changes (i.e., HbO increases, HbR decreases) reflect localized cortical activation.

With spatiotemporal resolution parameters falling between EEG and fMRI, fNIRS can provide millisecond-scale hemodynamic tracking with sub-centimeter spatial specificity (200), allowing researchers to both, accurately localize, and temporally map hemodynamic responses.

Wireless fNIRS devices further expand research capabilities by allowing neuroimaging during naturalistic movements (201) and engaging interactive tasks (202), which are particularly beneficial for individuals with attention impairments and motor control deficits (9). Neuroimaging possibilities with fNIRS include hyperscanning protocols that enable simultaneous measurement of brain activity across multiple individuals engaged in social interactions. This approach is particularly relevant for studying parent-child interactions in CP (203), and holds promise for promoting family-centered care by enhancing parent-child bonding during neurorehabilitation (204). An emerging application of fNIRS is its integration into brain-computer interface systems (205), opening new possibilities for communication and motor control in individuals with severe CP-related impairments (206). Additionally, fNIRS' flexible optode arrangements enhance customization for specific research applications (207) and improve signal quality (208). In combination with its low maintenance costs, portability and affordability, these factors make fNIRS uniquely suited for use in low-resource environments with high CP prevalence (75, 209).

Despite its various strengths, technical challenges to fNIRS use in CP remain. Limited penetration depth of near-infrared light (~10 mm) restricts imaging to superficial cortical structures, preventing analyses of subcortical structures such as the thalami, cerebellum, and basal nuclei that are commonly implicated in sensorimotor deficits in CP. Physiological confounders such as fluctuations in autonomic activity (210) and systemic hemodynamics (211) introduce signal contamination, necessitating sophisticated artifact correction methods (212). Another consideration is interindividual variability in light absorption, where scalp thickness, hair type, and melanin levels can influence optical signal quality (213, 214), potentially introducing biases in fNIRS data (215). Practical concerns include the prolonged setup time of fNIRS caps, combined with sensory hypersensitivity in some individuals with CP that may hinder compliance with fNIRS protocols, particularly in children with sensory processing difficulties. This may be compounded by the need for longer and more frequent trials to enhance reliability of fNIRS measurements due to a lower signal-to-noise ratio compared to fMRI (40). Physiological challenges in CP include the potential

for altered neurovascular coupling, the fundamental mechanism underlying fNIRS measurements. Brain injuries commonly associated with CP (e.g., PVL, perinatal stroke) can impair vascular autoregulation (216) and cerebrovascular integrity (217), complicating interpretation of hemodynamic responses (218). However, ongoing improvements in hardware, signal processing, and multimodal integration are expected to enhance sensitivity, reliability and applicability of fNIRS in both research and clinical settings.

Despite the widespread and growing use of fNIRS in neurodevelopmental disabilities, there is a lack of a summative review that comprehensively maps the feasibility, potential, utilization, and limitations related to the use of fNIRS in CP, which could impede adoption of this modality. In **Chapter 2**, I use a scoping review methodology to critically appraise the literature on the feasibility and current use of fNIRS to assess cortical activity, functional connectivity, and neuroplasticity in individuals with CP.

1.7. Literature review: Clinical and robotic assessments of upper limb function in CP

1.7.1. Clinical assessments of upper limb function in CP

Clinical assessments of upper limb function in CP have traditionally relied on observational, performance-based measures. The commonest categorization scheme for upper limb assessment in CP is derived from the International Classification of Functioning, Disability and Health (ICF) Biopsychosocial Model of Disability (World Health Organization) (219). The ICF classifies assessments into 3 major categories: (1) Body structure and function (impairment-based evaluations; e.g., range of motion, grip strength, sensory function, muscle tone), (2) Activity (what task(s) a child does (performance) or can do (capacity); e.g. tests of manual ability and dexterity), and (3) Participation (how a child functions in society and life situations; e.g. semi-structured interviews). As no upper limb outcome tool adequately captures each of the three ICF domains (219), current best-practice recommendations suggest a combined used of multiple tools to guide clinical decision-making. Since activity-based assessments are most commonly used (46%

of all assessments) (219) and considered the most important for pediatric upper limb function by expert professionals across rehabilitation disciplines (220), these will be the focus of the subsequent discussion. Importantly, the most widely used classification system for the upper limb (Manual Ability Classification System, MACS) (221) is often misrepresented as an outcome measure; however, this scale were developed for clinicians and parents to easily discriminate their child's ability to uses both their hands during daily manual tasks (222), was not intended to measure and is not sensitive to, changes in manual abilities (223).

Multiple assessment tools have been developed to evaluate the myriad and diverse prehensile, grasping, object manipulation and transport functional capabilities of the human hand (224). Gross manual ability is commonly evaluated with the Box and Block Test (BBT) (225), which is a timed, norm-referenced test that requires seated individuals to reach for and grasp 1-inch cubes from one side of a box and move them across a dividing barrier to the opposite side of the box. Gross manual ability is assessed as the total number of blocks transported in 1 minute, with population norms available above the age of 3 years (226). Test-retest reliability of the BBT ranges from good-excellent (227, 228), with weak long-term reliability and responsiveness (227) and a minimal clinically significant improvement of 7 blocks indicated for children with CP (228). Fine manual ability is most commonly assessed with the Purdue Pegboard Test (PPT) (229), which is also a timed, norm-referenced test that requires seated individuals to reach for, grasp and insert standard metal pins into predetermined slots on the pegboard. The number of pins inserted in 30 seconds provides a measure of fine unimanual ability, with bimanual components (synchronous, asynchronous) also assessed sequentially. The PPT has been validated for use in children (230), with asynchronous bimanual components placing heightened cognitive demands (231, 232) and providing a more detailed insight into fine motor abilities. However, the reliability, responsiveness and sensitivity to change of the PPT in CP is unknown, though it has been used as a criterion reference in the development of modified pegboard assessments in CP (233). Finally, complex dexterity and in-hand manipulation are assessed by the Functional Dexterity Test (FDT) (234), a

timed, norm-referenced test that requires seated individuals to reach for and lift wooden cylindrical pegs from slots on a wooden board, flip them upside down and reinsert them. Sixteen pegs are turned over in a predetermined pattern, with instructions to discourage forearm supination and avoid external support. While the FDT demonstrates excellent test-retest reliability in typically developing children (235), data confirming reliability, responsiveness and sensitivity to change in CP are currently lacking.

While clinical assessments play a critical role in characterizing impairments and tracking rehabilitation outcomes (236), their subjectivity, poor sensitivity, unidimensional focus renders them ineffectual at quantifying subtle deficits in motor control and coordination and capturing maladaptive compensatory behaviors. Observational assessments are prone to being influenced by individual, group, and interpersonal dynamics (237), with heightened fatigue (238, 239), low levels of engagement, and the use of compensatory movement strategies (240, 241) in individuals with CP reducing measurement accuracy and repeatability (224). Timed tests such as those detailed above prioritize speed over movement quality and coordination, providing little actionable insights into underlying neuromuscular deficits that can inform targeted therapies. Poor responsiveness is another major drawback of clinical assessments, with low sensitivity and high ceiling effects (242) of ordinal scaled tests preventing detection of both, minor deficits, and/or incremental but clinically meaningful functional improvements. Additionally, these evaluations provide unidimensional information of arm and hand use that does not account for the complex, multifactorial nature of upper limb dysfunction seen in CP. Abnormal cortical activation patterns observed in children with CP during the performance of simple upper limb tasks like grasping and simulated pouring point to central motor control deficits that may contribute to impaired arm use in CP (45). Novel assessments are required that can simultaneously evaluate the more pernicious issues of impaired motor planning, abnormal cortical activation patterns and disordered postural control that underlie poor manual abilities in children with CP (8, 45, 243).

1.7.2. Robotic assessments of upper limb function in CP

1.7.2.1 Overview of robotic assessments

Given these limitations, instrumented motion analysis and robotic assessments have emerged as promising tools to provide objective, high-resolution (≤ 0.1 mm) metrics of upper limb performance in CP. Scott and Dukelow (244) described two major categories of robots. Exoskeletons robots have joints that are aligned with body joint axes, allowing for joint motion to be tracked and quantified alongside hand movement during behavioral tasks, with added capabilities for limb weight support to minimize fatigue and overcome weakness. Conversely, end-point robots provide a cheaper and easy-to-use option, with a handle attachment for grasping and moving to assess hand kinematics but not joint-specific motion. Alongside movement quantification, these tools can provide semi- or fully automated control of limb movements, with options for applying directional and timed forces during free movement. This flexibility opens avenues for ecologically valid robotic assessments of force production, modulation, and coordination alongside detailed kinematics during tasks simulating real-world behaviors such as catching or hitting moving balls. Task difficulty can be modulated by varying target characteristics (e.g., speed, movement trajectories) or changing the applied force magnitude (e.g., higher forces for larger targets) or timing (e.g., during ongoing movement to evaluate motor adaptation). Robotic tools are commonly paired with monitors and audiovisual input/outputs for custom feedback options, with modern synchronization interfaces allowing integration with additional technologies such as eye-tracking systems, virtual or augmented reality, biomechanical tools (e.g., 3-dimensional motion capture, force plates), and mobile functional neuroimaging (e.g., EEG, fNIRS). High sampling rates coupled with near-instantaneous feedback and customizable task protocols opens further possibilities for novel multidimensional robotic assessments across functional domains. Robots have previously been used to assess motor capabilities (e.g., goal-directed reaching, bimanual coordination), sensory-perceptual abilities (e.g., proprioception, visuospatial attention) and cognitive proficiency (motor learning, attention, working memory, decision-

making), underscoring the vast potential of these novel tools to provide reliable, accurate, and sensitive insight into functional abilities of both neurotypical and neurodivergent populations.

A key advantage of robotic technologies is the wealth of richly detailed multidimensional information obtained from upper limb assessments such as reaching that, while behaviorally quite simplistic, require intricate coordination of vast neuronal architecture for movement planning (245), decision-making (246), coordination (247), execution (248), and learning (249). For example, Coderre et al. (250) described 10 key robot-derived metrics related to motor planning and preparedness, arm postural control, feedforward control, reactive feedback control, and overall motor performance during goal-directed reaching in individuals post-stroke. Robotic metrics demonstrated good reliability ($r \geq 0.7$ for 9/12 metrics), with differing patterns of impairments noted across topography of affection and subtle deficits detected in individuals with stroke whose overall performance and clinical assessment scores were comparable to neurotypical controls (250). This deep insight from the richness of robot-derived data holds potential for identifying individual impairment "fingerprints" that may inform targeted and personalized interventional approaches following neurological damage (244).

An interesting use of robotic outcomes was demonstrated by Bosecker et al. (251), who attempted to predict clinical assessment scores (e.g., Fugl-Myer Assessment, Manual muscle strength testing) in individuals with chronic stroke using combinations of robot-based kinetic and kinematic metrics obtained from 3 different robotic assessments. This novel strategy used principal component analyses and least squares multiple regression to reveal significant content redundancy between commonly used clinical assessments, while also providing interesting insights into the specific contributions of distinct kinematic factors to residual functional abilities in this group. More specific and reliable assessments reduce measurement variability and improve effect size estimates, with improved statistical power lowering sample size requirements for planned clinical trials (252), thus hastening translation of novel research paradigms and robotic tools.

Drawbacks to robotic use also require recognition. The most common concerns relate to high equipment, training and maintenance costs of robotic devices, restricting accessibility to well-resourced institutions in developed countries. Additional drawbacks include high dataset complexity, with even well-studied and standardized robotic assessments (253) providing a large number of movement-related metrics that may show redundancy and overlap, complicating interpretation and translation of outcomes for intervention planning (254). Data reduction methods such as principal component analyses performed alone (254) or in conjunction with confirmation factor analyses (255) can help alleviate these concerns, with reductions of up to 79% of behavioral data reported across robotic platforms (253). Limited evidence of translation of robot-identified deficits to real-world limitations in activity and participation is another concern, though a counter-argument may be that most clinical assessments for the latter are reliant on observer reports

1.7.2.2 Use of robotic assessments in CP

While robotic assessments have been widely applied in adult stroke rehabilitation, their uptake in CP has been relatively slow. Collectively, recent studies (13-25, 167, 256, 257) have demonstrated that robotic platforms offers high-resolution, objective, and ecologically valid assessments across a wide spectrum of sensory, motor, cognitive, and visuospatial functions in CP, with nearly all studies focused on those with unilateral impairments due to perinatal stroke or unilateral cerebral palsy. This preliminary work was followed by a collection of studies from the same research group that used the Kinematic Assessment of Normal and Altered Reaching Movements (KINARM) exoskeleton and end-point robotic devices to evaluate proprioception (both static joint position sense (13, 15, 167) and kinesthesia (15, 18)), visually-guided reaching (14, 16, 17, 21), bimanual coordination (20), visuospatial attention (21), and rapid motor decision-making (22). A separate study (19) integrated robotics and serious games to quantify motor function in children with CP, while more recent work extends the use of robotic assessments to adults with CP (24, 25).

Early studies by Kuczynski et al. (13, 15, 18) reported that proprioceptive impairments in static position sense and kinesthesia are more common and severe in those with arterial ischemic stroke (i.e., cortical lesions) compared to those with periventricular venous infarcts. Robotic outcomes outperformed clinical measures at detecting impairments, which were directly related to poor clinical outcomes for bimanual function ($\rho = -0.64$, $p < .01$) and dexterity ($\rho = -0.51$, $p < .01$), underscoring both the sensitivity and clinical utility of robotic assessments. Notably, proprioceptive deficits persisted with visual feedback (13, 18) in both types of perinatal stroke, and were often independent from reaching impairments (17), suggesting separate neural underpinnings. This contention was supported by evidence that robotic metrics of impaired proprioception were associated with lower sensory tract integrity of the lesioned hemisphere seen on diffusion weighted MRI in both perinatal stroke groups (15). These sensory tract alterations (e.g., lower fiber counts, worse diffusion metrics) were worse in those with arterial lesions and directly related to robotic metrics of proprioceptive deficits, but were not related to clinical assessments of proprioception, confirming the superiority of robots at detecting subtle deficits.

A possible limitation to the robotic tasks used in these studies was the use of the less affected arm movements to mirror those of the more affected arm that was moved passively by the robot. As the less affected upper limb in children with unilateral CP commonly shows some degree of motor impairment (258), this raised concerns that even minor motor involvement of the less affected upper limb could introduce error and bias. However, overall deficits and pattern of results did not change after removing subjects with motor involvement in the less affected limb (18), strengthening confidence in the study results. Zbytniewska et al. (259) attempted to overcome this potential drawback by using a single-joint end-effector robot to assess active and passive distal joint position sense at the metacarpophalangeal joint of the index finger. This novel assessment exhibited good test-retest reliability (ICC > 0.79) and sensitively distinguished children with unilateral CP from age-matched typically developing peers, supporting its utility in this group.

Early robotic assessment of motor functions in CP was reported by Masia et al. (23), who used a reaching protocol with an adaptive external force field to demonstrate inefficient motor control and poor motor adaptability in children with unilateral affection. The protocol revealed higher and more varied directional errors during the learning phase and poor error-based learning of compensatory behaviors in those with CP, with impaired motor learning compounded by their inability to scale arm acceleration and reaching speed in response to increased task demands posed by the external force field. Other researchers attempted to integrate serious games within robotic platforms, aiming to simultaneously assess and train motor function. Dehem et al. (19) validated a protocol that dynamically adjusted game difficulty based on the child's real-time performance metrics (e.g., velocity, movement straightness). This approach can both individualize task demands to maintain optimal challenge for improved motor learning, whilst concurrently improving therapy responsiveness and client motivation.

Robots have also proven useful in challenging traditional unilateral models of impairment following localized early brain injury. Kuczynski et al. (14) demonstrated that both upper limbs in children with unilateral perinatal stroke show significant deficits during visually guided reaching, including prolonged reaction time, inefficient movement paths, and slower hand speeds. Bilateral motor deficits were more prevalent and severe in those with arterial lesions than those with venous injuries, and robotic reaching deficits were also related to poor clinical test scores in the former group. Neural underpinnings of reaching deficits were explored in a subsequent study (16). Impaired reaching behaviors were linked to poor integrity of lesioned hemisphere CST motor fibers on diffusion tensor imaging, with altered CST microstructure in those with arterial lesions strongly related to multiple spatiotemporal parameters of impaired reaching (7 of 10 parameters; e.g., slowed reaction time, increased initial direction error, increased movement time). Extending this line of inquiry, Hawe et al. (21) used an ecologically valid, bimanual object hitting task in children with unilateral CP to detect motor deficits in both arms alongside subtle visuospatial asymmetries, with deficits similarly exaggerated in children with arterial perinatal strokes. Notably, they reported

motor output (hand speed, movement area) was relatively preserved in the CP cohort, with performance deficits driven primarily by visuospatial inattention, illustrating novel aspects of visuomotor integration previously unexplored in CP. In a further extension, Hawe et al. (22) then incorporated cognitive challenge into motor assessment through a robotic object hit-and-avoid task that used rapid motor decision-making ability to probe cognitive-motor interactions. Children with unilateral CP exhibited significant difficulty in inhibiting responses to distractors, striking more distractor non-targets than controls, suggestive of impaired inhibitory control and cognitive inflexibility. These deficits, exacerbated by task complexity, suggest that impaired executive function limits not only academic success but also motor execution in daily activities.

In summary, robotic assessments in CP have primarily focused on children with unilateral affection primarily arising from perinatal stroke of arterial or venous origin. Most studies support greater deficits in sensory, motor, visuospatial, and cognitive function in those with arterial lesions, with neurophysiological evidence linking sensorimotor deficits to microstructural alterations in sensory (Dorsal column medial lemniscus) and motor (CST) pathways. Compared to standard clinical assessments, robotic metrics displayed stronger and more consistent associations with neurophysiological abnormalities, highlighting the potential for combined neuroimaging-robotics evaluations to illustrate structure-function relationships. These studies support the use of robotic assessments as highly sensitive, valid, and reliable tools to detect subtle impairments and identify novel prognostic and therapeutic biomarkers for personalized intervention planning in CP. However, no studies have integrated mobile functional neuroimaging tools with robotics to concurrently assess neurophysiological dynamics and motor behavior during goal-directed tasks in CP. Integrating fNIRS with robotics can provide insights into how brain-behavior links impact dysfunctional motor behaviors and aberrant cognitive-motor interactions.

1.8. Literature review: Moving target interception in CP

1.8.1 Interception as a model of motor control

The ability to intercept a moving target is a highly evolved motor behavior supported by vast neural architecture that regulates complex interactions and real-time coordination between the sensory, perceptual, visual, and motor systems. Catching or hitting a moving ball requires judgement of the ball's spatiotemporal properties (location, speed, direction of movement) and precise timing, coordination and coupling of eye-hand movements to reach the ball's predicted future location. Eye movements that visually track and predict target location are integral to successful interception, with their role and impact increasing as target motion becomes increasingly unpredictable (260). Object properties are concurrently processed via the dual visual processing streams (261), with the dorsal "vision-for-action" stream directing the control of goal-directed interactions with the object, while the ventral "vision-for-perception" stream incorporates sensory information to form a perceptual understanding of the target object (262). Both streams avail the same visual inputs, but differ in the manner and purpose of subsequent transformation of visual information into coordinating purposeful motor actions (dorsal stream) or developing a perceptual understanding of object-environment properties and relationships (ventral stream) (263). Notably, these streams display multiple interconnections and both influence and interact with each other during real-world movements (264), with visual cues influencing eye movements (265) as well as decision-making (266) during interception.

The types and utility of visual cues in reaching was explored by van Hof et al. (267), who examined developmental changes in interceptive behaviors towards approaching toys in typically developing infants aged 3-9 months. Two distinct modes of visual cue usage were identified: younger infants lacking perceptual accuracy tended to employ a distance strategy to initiate reaches when the toy was a fixed distance away, while older infants with more refined perceptual judgement used an adaptive time strategy to begin reaching when toys were a constant duration away. The authors proposed the time strategy was more generalizable across tasks and environmental contexts

than the distance strategy, with the latter more commonly observed in infants with worse catching ability (268). These reports underscore the strong perception-action coupling that underlies visual control of goal-directed actions such as interception demonstrates high complexity even early in infancy.

In contrast, kinematic reaching strategies to intercept a moving object appear simple but provide deep insights into sensorimotor integration and visuomotor coordination during goal-directed behaviors. Reaching toward the target's current (instantaneous) position would result in a continually lagging hand trajectory due to visuomotor processing delays of 100-200 ms (269), while directing hand movement ahead of the target's current position would require using visual cues of target speed and trajectory to continuously update the target's predicted position (270). Alternative strategies that reduce computational complexity involve aiming straight towards some fixed interception point (271), or adaptively maintaining a constant bearing angle between the individual's trajectory and target position by adjusting arm movement speed and/or direction (272). The latter has been touted as a promising interceptive strategy commonly used by both typically developing children and neurotypical adults when target trajectories follow specified patterns (273, 274); however, it poorly generalizes to unpredictable conditions, such as when targets suddenly change position (275), accelerate and decelerate (276), when obstacles are present, or when vision is occluded (277).

This complexity is further reflected in the multiple attempts made to model interceptive behaviors. Zago et al. (278) posited that interception use internal models of the environment to predict the trajectory of moving targets, combining multisensory information with prior knowledge to guide action. These internal models are inherently approximate and reliant on educated guesses that optimize performance despite sensory noise and motor delays. Using evidence of poor visual dependency in unpredictable visual environments (e.g., visual occlusion), Zhao and Warren (279) modeled interceptive behaviors in as a combination of strong, vision-dependent 'online' models with weak, heuristic 'offline' strategies which use prior experience of how environment and tasks

are interlinked to provide compensatory spatial maps in the absence of predictable visual inputs. Fiehler et al. (271) argued that interceptive behaviors represent an output of continual predictive processes that govern both eye movements (e.g., predicting gaze location following a saccade) and interceptive arm movements (e.g., anticipating future hand position or expected sensory feedback to correct ongoing movement or improve future predictions). Conversely, Savelsbergh et al. (30) argue that most computational approaches to model interceptive actions offer poor clinical translation. They propose an alternative perception-action coupling approach (280) suggesting interceptive behaviors arise as self-organized motor solutions from complex interactions of individual characteristics (e.g., motivation, strength, spasticity), social-environmental context (e.g., visual cues, target spatiotemporal properties, distractors), and task constraints (e.g., time constraints) (281).

Beyond these theoretical considerations, common aspects of interceptive behaviors, including anticipatory control, sensorimotor integration, and adaptability to dynamic contexts, make them ideal for investigating motor control impairments in CP. Performance on interception tasks can illuminate specific deficits in anticipatory motor control, sensory integration, and action planning, contributing to our understanding of how early brain injury impacts predictive strategies in this group.

1.8.2 Use of moving target interception to investigate motor function in CP

Most studies using interception-based task protocols have been conducted in children with unilateral spastic CP using both locomotor interception and manual interception paradigms. Ricken et al. (282) reported beneficial impacts of external time constraints (i.e., intercepting a moving ball) on impaired arm kinematics during a walk-and-intercept task. Faster decelerations and wrist velocities reported alongside increased elbow excursion under time constraints compared to intercepting a stationary target suggests imposing time restrictions can trigger latent adaptive motor behaviors with the more affected arm. Children with CP also adapted their gait kinematics by

slowing down when walking to intercept instead of prolonging their reach duration, contrasting with previous work (283) that reported exaggerated trunk movements to compensate for slower and more segmented movements of the more impaired arm when intercepting from a standing position. Extending this line of work, Ricken et al. (284) modulated external time constraints duration (i.e., target speed) during the same walk-and-intercept task, reporting lower interception success and greater trunk compensation with faster target velocities. However, a notable increase in walking velocity above pre-trial peak values, coupled with improved shoulder and elbow excursions in the more impaired arm, highlights the preserved ability to adapt motor behaviors to higher task demands in this group.

The use and impact of visual cues on interception performance in CP was investigated across a trio of studies (285-287) by the same research group. Similar to typically developing children (274) and neurotypical adults (273), children with unilateral CP also used a constant bearing angle visual strategy (272) during a walk-and-intercept task (285), with greater variability in bearing angles occurring alongside notable adaptations to sustain motor performance with the more impaired arm. To compensate for slower movements, children with CP increased walking speed at gait initiation before slowing down at the late approach phase to allow more time ('safety margin') to execute accurate interceptive movements with the more affected arm. Van Kampen et al. (286) extended this line of inquiry to interrogate the impact of side of brain injury (i.e., left vs right hemisphere lesion) on visual interceptive strategy (i.e., time vs distance strategy of van Hof et al. (267)). Children with right hemispheric lesions followed typically developing children in using the developmentally mature time strategy. Conversely, most children with left hemisphere lesions (5 of 9) used the developmentally immature distance strategy observed in young infants with poor perceptual judgement. Given the less refined distance strategy is related to poor catching skills (268) and more simplistic predictive planning, early developmental damage to the left hemisphere may damage the left hemisphere-lateralized neural networks mediating action planning and tool use (288) resulting in impaired visuomotor planning and prediction. This contention gained

support from a follow-up study (287) assessing gaze behaviors during the walk-and-intercept task in the same group. Altered gaze behaviors were observed during the initial approach phase in children with left-sided lesions compared to those with right-sided lesions, though interception accuracy did not differ across the two groups, underscoring the need for more detailed neurophysiological assessments to better characterize these structure-function relationships.

Distinct from the locomotor interception studies described above, van Thiel et al. (289) examined how children with unilateral CP perform fast unimanual movements to hit stationary targets or intercept moving targets under external time constraints from varying target velocities. Compared to stationary reaching, moving targets provoked faster reaction and movement times, with similar performance outcomes (i.e., accuracy rate and end-point errors) and peak velocities in both groups, further supporting the positive impact of external time constraints on kinematic outcomes. Interestingly, reaction time did not vary across increasing target velocity in those with CP, suggesting preserved prospective motor control despite their unilateral motor impairment. However, the presence of subtle bilateral motor deficits within this cohort highlights the complexity of motor system involvement even in individuals with unilateral affection. Importantly, integrating such kinematic paradigms with mobile functional neuroimaging could offer critical insights into the underlying cognitive planning and inhibitory control mechanisms. Given the variability in motor performance despite preserved reaction timing, concurrently investigating prefrontal cortex activation during sensitive robotics assessment of upper limb function may yield critical insights into compensatory versus maladaptive neural strategies, with implications for targeted therapeutic interventions.

1.9. Literature review: Prefrontal cortex function in CP: Theoretical frameworks

The prefrontal cortex (PFC) represents the most evolutionarily advanced cortical structure found only in primates (290) and attempts to define and categorize its diverse functions have spurred debate and discourse spanning several decades (291). While some experts describe the

principal role of the PFC as "the representation and execution of new forms of organized goal-directed action" (292), others view the PFC's principal role as selecting task-relevant sensory cues and specifying the goal of motor behaviors (291). The latter functions are posited to occur via attentional enhancement, with the PFC selectively enhancing activity in task-specific sensory and premotor association areas via intracortical connections.

The PFC's ability to modulate output across sensorimotor networks underlies its role in executive functions such as executive attention, working memory, cognitive flexibility, and inhibitory control (293). Given the close interlinkage of cognition and motor functions during development (280) and the PFC's posited position atop sensory-motor and action neural hierarchies (294), some authors have attempted to reframe the PFC's myriad functions in light of motor behaviors and consequences (295, 296). Fuster (53) contextualized the role of the PFC within the perception-action cyclical framework, where it serves predictive and preadaptive functions to temporally organize goal-directed actions. Specifically, the PFC plays a central role in action planning, pulling in perceptual information and prior knowledge from the environment and memory via neural networks ('cognits' (297)) in the posterior association cortices, and using this information to plan motor actions whilst concurrently predicting and preparing (i.e., preadapting) the sensorimotor systems for the expected consequences of the intended action (52). By planning and predicting actions and anticipated feedback, the PFC can coordinate sensorimotor integration, track behavioral outcomes, and drive behavioral corrections to achieve action goals.

Distinct from Fuster and others contention that vast, distributed neural networks (cognits) mediate the PFC's diverse functions, neuroeconomic theorists have positioned the PFC as a master central executive responsible for regulating the allocation of the brain's limited neurometabolic resources among multiple competing systems (298). This theory assumes a fixed availability of neural resources (e.g., glucose, oxygen) and models resource demands across brain regions as a function of task complexity. Areas mediating computationally complex behaviors present a greater need for resources, with performance deficits associated with increased deficits between resource

supply and demand. Once a system depletes its resources, the PFC's role as central executive is to 'decide' how to allocate resources across competing neural systems to ensure optimal behavioral outcomes and task goals are met (299). While speculative, this proposition has obvious parallels with Fuster et al. (292) and Passingham et al.'s (291) contention that the PFC employs directed attentional shifts (i.e., attentional or task 'sets' (300)) to mediate top-down, bidirectional control of sensorimotor system during goal-direction actions.

Other researchers have attempted to probe the role of the PFC in motor function during both acute (301) and exhaustive exercise (302). Based on similar principles of constrained resource availability and competitive allocation, Dietrich's transient hypofrontality hypothesis (303) proposes brain activity is proportionally decreased in areas not directly engaged in motor execution or control (e.g., PFC). This reduction in PFC activity is posited to maintain optimal motor performance during acute exercise or intense bouts of physical activity, with at least some negative impact on PFC-associated executive functions reported across studies (304).

Together, these theoretical frameworks underscore the PFC's integral role in dynamically coordinating cognitive and motor demands, particularly under conditions of limited neural resources or heightened task complexity. Yet, despite these insights, little is known about how PFC-mediated control of sensorimotor systems may be altered following early brain injuries. **Chapter 2** provides a detailed review of fNIRS studies that have examined PFC activity during functional tasks performance in individuals with CP. Building on this foundation, emerging approaches that integrate robotic assessments with mobile functional neuroimaging (e.g., (305, 306)) offer a promising avenue to investigate how PFC activity patterns contribute to upper limb motor impairments in this population.

CHAPTER 2

ASSESSMENT OF CORTICAL ACTIVITY, FUNCTIONAL CONNECTIVITY, AND NEUROPLASTICITY IN CEREBRAL PALSY USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY: A SCOPING REVIEW

[1] Khan, O.A., Rahman, S., Baduni. K., Modlesky, C.M. 2025. *Developmental Medicine and Child Neurology*. 00: 1–17. https://doi.org/10.1111/dmcn.16238

Abstract

Aim: To map and critically appraise the literature on the feasibility and current use of functional near-infrared spectroscopy (fNIRS) to assess cortical activity, functional connectivity, and neuroplasticity in individuals with cerebral palsy (CP).

Method: A scoping review methodology was prospectively registered and reported following Preferred Reporting Items for Systematic review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines. A systematic search was conducted in four databases. Empirical studies using fNIRS to assess neural activity, functional connectivity, or neuroplasticity in individuals with CP aged 3 years or older were included.

Results: Sixteen studies met the inclusion criteria. Individuals with CP (age range = 3–43 years; 70% unilateral CP) underwent fNIRS-based assessment for task-evoked activity (studies [*n*] = 15) and/or resting-state functional connectivity (*n* = 3). Preliminary observations suggest greater magnitude, extent, and ipsilateral hemispheric lateralization of sensorimotor cortex activity in CP, while magnitude and patterns of prefrontal cortex activity in CP appear dependent on task demands. Normalization of fNIRS-based activity metrics observed postintervention (*n* = 3) paralleled improvements in functional outcomes, highlighting their potential as promising biomarkers for functional gains in CP.

Interpretation: This review details the use of fNIRS in CP, highlights research gaps and technical limitations, and offers recommendations to support fNIRS implementation for ecologically valid functional neuroimaging in individuals with CP.

2.1. Introduction

A majority of children with cerebral palsy (CP) present abnormal findings on neuroradiological examinations (307), with lesions identified through structural magnetic resonance imaging (MRI) often corresponding to patterns and distribution of sensorimotor impairments. For example, focal vascular lesions are commonly observed as perinatal stroke in unilateral CP (91), while diffuse bilateral white matter injury (e.g., periventricular leukomalacia) is most frequent in bilateral CP, and grey matter lesions are often associated with dyskinetic CP (308). However, at least 10-15% of children with CP have normal MRI scans (90, 91), and abnormal findings do not consistently relate to clinical outcomes in CP (151, 309) due to the complex interactions between lesion type, timing, location, and extent (150, 310-312). The exaggerated potential for neuroplasticity in the early years of life (Kennard principle) (94, 313), individual genetic constitutions (314) and epigenetic variance (315), and lived experiences further contribute to the heterogeneity in brain structure-function relationships in CP (161, 316, 317).

Functional neuroimaging can provide greater insights into neurophysiological dynamics during functional tasks (162, 163). The most commonly used functional neuroimaging modality in CP is functional MRI (318), which measures changes in blood oxygenation levels (BOLD response) to capture brain activity during tasks (task-evoked activation, e.g., (319)), and identify functionally connected brain regions at rest (resting-state functional connectivity, e.g., (320)). Functional MRI has been used in CP to investigate adaptive plasticity following intervention (166, 321), and resting-state functional connectivity in the sensorimotor (322, 323) and language neural networks (324) and their association with clinical outcomes (167). Alternative modalities, such as electroencephalography (EEG) and magnetoencephalography (MEG), offer superior temporal resolutions compared to MRI and directly capture electrical activity in neuronal populations. Studies using EEG in CP reported reduced activity at specific frequencies (mu-band (171)) in the ipsilesional sensorimotor cortex during upper limb tasks (reach-to-grasp (172), isometric wrist extension (173), hand squeezing (157)) and heightened bilateral activity during treadmill walking

(174). Altered dynamics of the somatosensory (178), visual (175-177), and sensorimotor cortices (179) identified through MEG studies in CP shed light on impaired motor planning (180) and execution, with MEG outcomes potentially sensitive to change following intervention (181, 182).

Despite these promising observations, practical concerns (e.g., scanner constraints, signal noise and high costs) limit the use of these modalities in children (169, 170). While efforts to improve scanner-based experiences have increased acceptance and completion rates (185, 186), concerns persists about the effectiveness of in-scanner strategies to reduce movement artifacts (325), and of motion correction strategies during data processing (326). These issues are magnified in individuals with CP, who exhibit cognitive, visuospatial and sensorimotor impairments (9, 327) that renders them unable or unwilling to remain still, sustain attention, or comply with task instructions during repetitive experimental assessments (184). For example, children with even mild manual impairments struggle to comply with simple hand squeezing tasks during functional MRI (157). Additionally, individuals with ataxic or dyskinetic CP who experience involuntary movements, are underrepresented in neuroimaging studies (183), resulting in selection bias and limited generalizability of neuroimaging findings (187). These observations highlight the need for child-friendly, non-invasive functional neuroimaging tools that can incorporate engaging and ecologically valid methods.

Functional near-infrared spectroscopy (fNIRS) is a relatively inexpensive, portable, and non-invasive functional neuroimaging tool with great potential for assessing brain activity in CP. Like functional MRI, fNIRS relies on neurovascular coupling, or increased blood flow (reactive hyperemia) to active neural areas in response to metabolic demand (197), to provide an indirect measure of neural activity (195, 196). Near-infrared light of specific wavelengths (optical window, 650-900 nm (198)) is emitted through optodes placed in contact with the scalp, typically via a flexible cap (**Figure 2.1**). This light penetrates 1-2 cm into the underlying tissue, being reflected, scattered, and absorbed by oxyhemoglobin and deoxyhemoglobin in the outer 5-10 mm rim of cerebral cortex (328). Emergent light is captured by detectors, and attenuation of light intensity is

used to quantify relative changes in hemoglobin concentrations through the modified Beer-Lambert Law (199). Cortical activity is indirectly reflected by an increase in oxyhemoglobin and a concurrent, smaller decrease in deoxyhemoglobin concentration, with a net increase in total hemoglobin concentration (38).

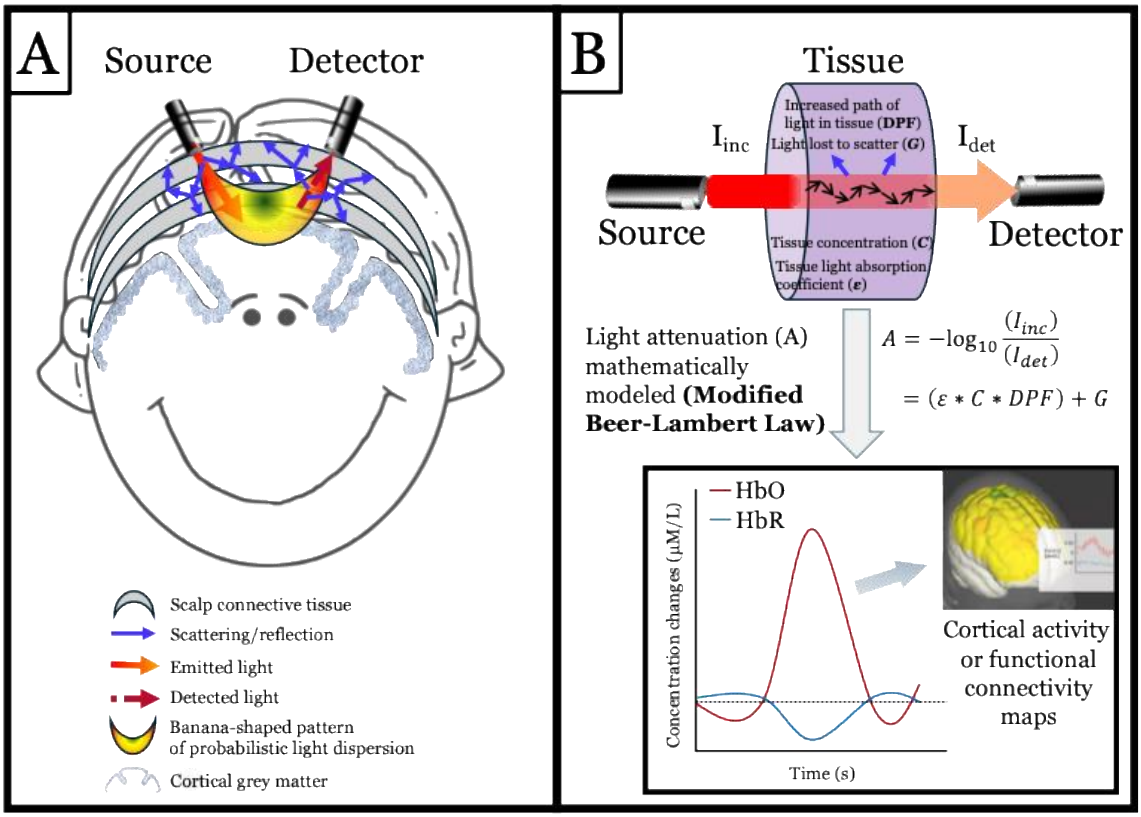

Figure 2.1. Schematic illustration of the principles of fNIRS measurement (A). Near-infrared light passes through scalp connective tissues, undergoing scattering, reflection and absorption along its probabilistic banana-shaped path through cortical tissue, before being reflected out to be captured by detectors placed at the scalp. (B) Decreased light intensity is mathematically modelled (Modified Beer-Lambert Law) using estimates of tissue concentrations (C) and light scattering (G), absorption (ε) and refraction (DPF, differential pathlength factor) to obtain estimates of relative changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentration. These changes are surrogate markers of cortical activity, with modern software providing real-time feedback of cortical activity and functional connectivity at rest or during functional task performance.

Features of fNIRS that make it particularly suited for use in children and adults with neurodevelopmental disorders such as CP are detailed in **Table 2.1.** Briefly, fNIRS provides higher spatial resolution than EEG and better temporal resolution than functional MRI, allowing for

accurate localization and temporal characterization of cortical activity (200). Wireless fNIRS devices enable mobile neuroimaging in natural settings (201), facilitating ecologically valid tasks that optimize engagement (202), an especially important consideration in individuals with CP exhibiting cognitive and attention deficits (9). Notably, functional task contexts provoke improved postural control (329) and altered cortical activation patterns in those with CP compared to conventional experimental tasks such as finger tapping (330). Additionally, fNIRS offer greater methodological flexibility, customizable optode template arrangements (207), low cost, and minimal maintenance, making it an ideal neuroimaging tool in low-resource settings of low- and middle-income countries that show greater prevalence of CP (75).

Table 2.1: Non-invasive functional neuroimaging modalities

Modality	*Typical resolution (Spatial; Temporal)	Movement tolerance; Safety; Cost	Setting	Additional comments
fMRI	3-12 mm (high); 2-4 s (low)	[a]Low; High; High	Scanner-based; Loud scans with limited limb motion	Indirect measure of neural activity (BOLD response with ∂HbR only); Whole-brain and white matter tractography; Can detect subcortical neural activity
MEG	3-5 mm (high); <1 ms (very high)	Low; High; Very high	Scanner-based via helmet with helium-encased sensors; Silent scan	Direct measure of neural activity (ultra-minute magnetic fields, 10^{-15} T); No reference electrode; Whole-brain and subcortical neural activity detection
EEG	≥1 cm (low); ≤1 ms (very high)	Low-moderate; High; Low	Semi-mobile via cap-based using gel adhesive; Silent scan	Direct measure of neural activity; Reference electrode needed; Cap and gel-induced discomfort; Whole-head with high-density templates; Sensitive to contraction & motion artifact
fNIRS	0.5 - 2 cm (moderate); 10 ms – 1 s (moderate)	Moderate-high; Very high; Low	Freely mobile if via wireless cap-based optodes; Silent scan	Indirect measure of neural activity (neurovascular coupling: ∂HbO and ∂HbR); Whole-head with high-density templates; Low optical penetration limits detection of activity to cerebral cortex; ^Discomfort from cap & optode

BOLD, blood oxygen level dependent; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; ∂HbO, change in oxyhemoglobin concentration; ∂HbR, change in deoxyhemoglobin concentration; MEG, magnetoencephalography. *Not theoretical limits, but dependent on acquisition and processing protocols; ^System-dependent; [a]New strategies in development to improve tolerance to movement (e.g. real-time head motion feedback in CP (168)).

A major drawback of fNIRS is its limited penetration depth, which prevents the assessment of neural activity below the outer 5-10 mm cortical grey matter. This precludes neuroimaging of

deep grey matter structures (e.g., basal nuclei, thalami) or deeper temporal lobe structures (e.g., hippocampi) that are involved in more extensive lesions in CP (105). Another shortcoming is the susceptibility of fNIRS signal to contamination from task-induced and/or spontaneous changes in systemic physiology such as fluctuations in heart rate, respiration, blood pressure, or autonomic activity (331). A significant portion of near-infrared light is absorbed by superficial, extracerebral tissues that are sensitive to non-neuronal physiology (211), necessitating additional signal processing to account for this contamination. Technical challenges arise with fNIRS data collection in individuals with thick or curly hair that can hinder scalp-optode contact. Additionally, individuals with darker skin experience reduced penetration depth of near-infrared light (213, 214), potentially introducing systemic biases in fNIRS results (215). The fNIRS community is aware of these limitations (332), with efforts to address technical shortcoming (333, 334), improve accessibility and tackle equity challenges in fNIRS research spurring initiatives such as the BRIGHT project, that uses fNIRS to assess neurodevelopment in infants in The Gambia (209).

Previous reviews of neuroimaging findings in CP have primarily focused on structural brain lesions (335, 336) or connectivity (183), with task-based functional neuroimaging reviews generally limited to conventional scanner-based modalities such as functional MRI (159, 163). While several reviews have detailed the use of fNIRS in typically developing children (40) and those with other neurodevelopmental disorders (337, 338), a comprehensive review specifically addressing the potential, limitations, and applications of fNIRS in CP is lacking, which may discourage adoption of this modality in research and clinical settings (332). To this end, this scoping review aims to map and critically appraise the literature on the feasibility and current use of fNIRS to assess cortical activity, functional connectivity, and neuroplasticity in individuals with CP.

2.2. Methods

A scoping review was conducted to synthesize existing knowledge on the use of fNIRS neuroimaging in CP (1, 339), map current practices and highlight research gaps (340). In

accordance with evidence-based principles (341), five key steps were included: research question identification, literature identification, study selection, data extraction, and evidence synthesis. Results were reported following PRISMA-ScR guidelines (342). The study protocol was registered on the Open Science Framework (osf.io/f3u8b).

2.2.1. Research Question(s):

How has fNIRS been used to assess cortical activity, functional connectivity or neuroplasticity in children and adults with CP? What are the methodological characteristics (sample characteristics, experimental protocols, processing pipelines and analyses algorithms) of studies that have used fNIRS in CP? What is the feasibility, potential, and limitations related to the use of fNIRS in CP?

2.2.2. Identification of Relevant Studies

A systematic search was conducted in PubMed, Web of Science, CINAHL (via EBSCOHost), and PsycINFO (via EBSCOHost) following the Joanna Briggs Institute format (343) (**Table 2.2**). Key terms were piloted on PubMed for sensitivity in detecting relevant studies, with the search strategy (**Table 2.S1**) finalized in consultation with an academic librarian and translated across databases. Hand searching strategies included reviews of reference lists and citation tracking using Google Scholar and Lens (344). No date or language restrictions were applied, and searches were updated on July 18, 2024. In line with previous scoping reviews (345-347), grey literature (**Table 2.S2)**, abstracts, conference proceedings, and opinion pieces were not included, to focus on empirical, peer-reviewed literature and prevent "double-counting" of studies.

Table 2.2: Systematic search components

Component	Search criteria
Population	All children and adults diagnosed with cerebral palsy (CP) of any etiological origin; includes pre-, peri- or post-natal stroke; All topographical and phenomenological distributions included (unilateral-bilateral; hemi-/diplegia; no restriction on spastic-ataxic-dyskinetic-hypotonic-mixed tone presence)
Concept	Any aspect of brain function, dysfunction, connectivity or plasticity captured specifically using optical functional neuroimaging via functional near-infrared spectroscopy (fNIRS)
Context	All geographical locations; All genders and races/ethnicities included; Clinical, academic and/or research settings accepted; No language restrictions implemented.

2.2.3. Study Selection

Eligible reports were imported into EndNote (v.20; Clarivate, Philadelphia, PA) and Rayyan (348). Duplicates were manually removed, and titles and abstracts were independently screened by 3 reviewers (OK, SR, KB). Criteria for study inclusion were: (a) Empirical human stud using fNIRS to assess brain activity, functional connectivity or neuroplasticity; (b) Studies where >50% of the sample comprised children (aged ≥ 3 years, after complete myelination in infancy (349)) or adults with CP. No demographic or geographic restrictions were imposed. Studies not reporting task-evoked or resting-state fNIRS outcomes, or those focusing on neurodevelopmental disorders other than CP were excluded. Full-texts were reviewed independently by two reviewers (OK, SR), with disagreements through discussion, or through consultation with a third reviewer (KB).

2.2.4. Data Extraction

A data extraction table was designed prior to study selection and iteratively refined during full-text review to ensure completeness of extracted information (345). Two reviewers (OK, SR) performed data charting with pseudorandom assignment ensuring studies from the same group were reviewed by one reviewer for consistency (346). One reviewer (OK) validated accuracy of data extraction for all studies.

2.2.5. Evidence synthesis

Data were tabulated and categorized by study background, sample characteristics, experimental procedures, fNIRS parameters, and primary findings. Research trends and clinical implications were highlighted, with recommendations proposed for future fNIRS research in CP.

2.2.6. Critical appraisal of included studies

In line with previous fNIRS work (345), study quality was appraised by three reviewers (OK, SR, KB) using the adapted 15-item Down's and Black assessment tool for non-randomized studies (350) (**Table 2.S3**), with consensus achieved through discussion. Quality was rated as low (<60%), moderate (60-74%) or high (≥75%), based on proportion of criteria met.

2.3. Results

From 112 studies identified through searches, 42 duplicates and 41 irrelevant studies were removed. Full text review of 29 studies resulted in the inclusion of 16 studies for analyses. **Figure 2.2** illustrates the study selection process.

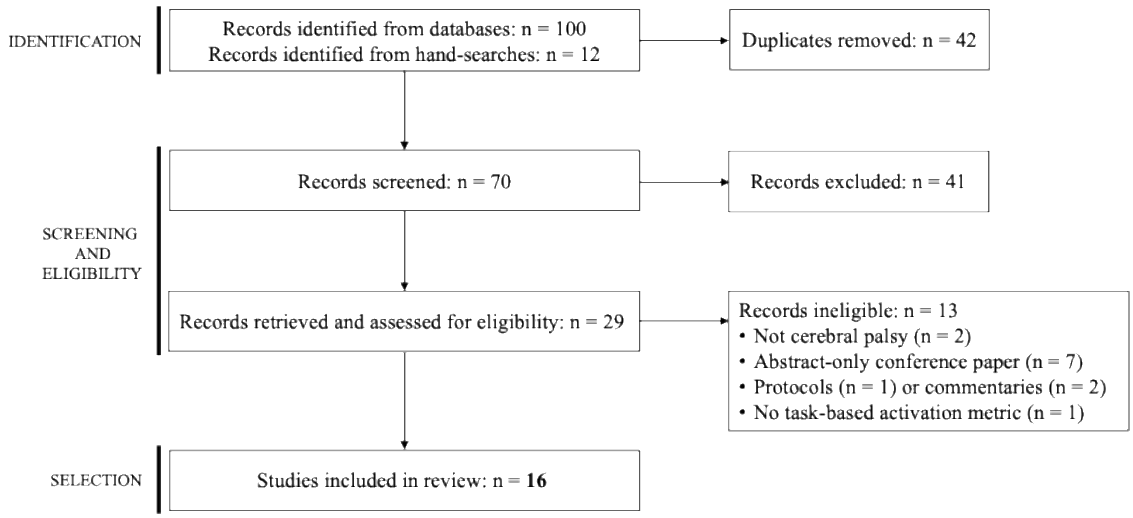

Figure 2.2: PRISMA-ScR flow diagram.

2.3.1. Study quality and background

Using the modified Downs & Black checklist (**Table 2.S4**), study quality scores ranged from 53% to 100%, with an average score of 84%. Three studies (42, 43, 351) scored 60-74% (moderate quality), one study (352) scored < 60% (poor quality), and the other twelve studies scored ≥75% (high quality). The lowest scoring item assessed external validity ("Were subjects representative of the population", 44%), with similarly low scores for questions assessing confounding ("Were subjects recruited from the same population?", 56%) and internal validity ("Were subjects recruited over the same period?", 50%).

2.3.2. Study background and sample characteristics

Study settings (**Table 2.S5)** indicate most studies (n=13) were conducted in the United States, with two studies in China (351, 353) and one in Italy (56). All studies were published during

the past 15 years (2010-2024), and were in English. Most studies (n=13) were observational, with three interventional studies including pre-post assessments (59), one including a mid-intervention assessment (56) and another with a 6-month follow-up (43). A priori power analyses was reported in only one study (58), while two studies (43, 44) used *post-hoc* analyses to assess fNIRS's sensitivity at detecting group differences. Attrition rates (10-33%) were reported in six studies. One study excluded 20% of data (2 out of 10 subjects) *post-hoc* due to large lesions observed in the cortical regions of interest on structural MRI (45).

Participant characteristics are also detailed in **Table 2.S5**. Across 16 studies, 158 individuals with CP were assessed using fNIRS (sample size = 2-24), with 70% displaying unilateral affection (i.e., UCP). Participant age ranged from 3-43 y, with twelve studies recruiting only children, three studies including both children and adults (45, 47, 48), and one pilot study assessing two adults with CP (352). Structural brain imaging confirmed brain injury in seven studies, or was inferred through inclusion/exclusion criteria (46, 57-59). Nine studies described brain pathology, with six studies specifying injury type (e.g., perinatal stroke, periventricular leukomalacia) and three studies reported lesion location (e.g., subcortical or cortical lesion) (41, 43, 44). Functional classification varied by type of experimental task. Seven of the 11 studies incorporating an upper limb task documented Manual Ability Classification System (MACS) levels. Most participants displayed mild impairment (MACS levels I-II: n=46, 63%) or moderate impairment (MACS levels III-IV: n=26, 36%), and one study included a subject with severe impairment (MACS level V) (59). Gross Motor Function Classification System (GMFCS) levels were consistently reported across studies using a lower limb or whole-body task (46-48, 56, 135, 353), with most participants displaying mild-to-moderate impairments (GMFCS levels I-III: n=71, 87%) and severe impairments less frequent (GMFCS level IV: n=10; GMFCS level V: n=1) (56, 353). Muscle tone abnormality (primarily spasticity) was reported eight studies, with two studies reported limb dystonia (45, 48). Mirror movements were documented in four studies (41, 42, 47, 48), with one study focusing on this phenomenon (42).

2.3.3. Experimental procedures

Experimental procedures are summarized in **Table 2.S6**. Most studies employed motor tasks, except for three studies that used cognitive-motor dual-tasks involving varying cognitive demands (57, 59) or concurrent postural challenge (58). Upper limb tasks included unimanual protocols such as finger tapping (41-44), ball grasp-and-drop (352) and shape-matching (57-59)), as well as bimanual protocols such as ball grasp-and-squeeze and simulated pouring (45) and machine-assisted arm cycling (351). One study combined unimanual and bimanual tasks (47). Lower limb tasks included functional mobility (treadmill walking (46), robot-assisted gait training (56), functional strength (progressive lateral step-up) test (135)), and seated protocols such as passive cycling (353), active cycling (48) and single-joint movements (47, 48). Only one study combined upper and lower limb tasks (47).

2.3.4. Major study findings

Major research questions and primary findings of each study are presented in **Table 2.S7**.

2.3.4.1. Task-evoked sensorimotor cortex activity in CP

Early fNIRS studies highlighted altered patterns of local hemodynamic activity in children with unilateral CP (UCP) with lower time-to-peak activity (41) and time-to-peak activity/total activation duration ratios (44) consistently observed at 2 months and sensitive at distinguishing UCP from age-matched typically developing children (41, 44). The same research group identified contributions of mirror movements to bilateral sensorimotor cortex (SMC) activity in UCP during unimanual tasks (42), with methods proposed to isolate these signal contaminants. Age-related variability in SMC hemispheric laterality was greater in children with UCP, who displayed bilateral SMC activation, unlike contralateral SMC activity displayed by typically developing children older than 7 years (41). Following intensive constraint-induced movement therapy (CIMT), acute changes in local hemodynamics in children with UCP were sustained at 6-month follow-up, while acute change in SMC laterality (increased contralateral SMC activity) was not maintained, and

was related to better unimanual, but worse bimanual function (43). Heightened SMC activity was also observed in adolescents and young adults with UCP during bimanual tasks (45), with asymmetric tasks evoking more exaggerated and lateralized SMC activity that were linked to increased muscle co-activation and better daily function on the PEDI-CAT, respectively.

Few fNIRS studies assessed SMC activity in individuals with BCP displaying bilateral affection. One exploratory study (46) reported greater SMC and superior parietal lobule activity in BCP (n=4) than controls during treadmill walking. Increased activity in the combined groups was related to greater variability in temporal gait parameters, suggesting heightened neural demands to maintain ongoing gait trajectories. Another study reported greater SMC activity in older adults with BCP during lower limb tasks (48), with activity scaling with higher GMFCS levels and greater muscle activation. Increased SMC activity during non-dominant ankle dorsiflexion was also related to worse selective motor control, and lower walking ability and mobility scores on the ABILOCO and PEDI-CAT, respectively. The only study comparing SMC activity in UCP and BCP (47) reported excessive activity in both groups compared to controls, with activity scaling with increasing functional impairment (higher MACS, GMFCS levels). Differences between CP groups were task-dependent. During non-dominant hand squeeze, SMC activity was greatest in individuals with UCP and those with more impaired manual abilities (MACS level III), with a positive relationship observed between SMC activity and MACS level. During non-dominant ankle dorsiflexion, SMC activity was greatest in individuals with BCP and those with more impaired gross motor function (GMFCS level III), with a similar positive association observed between SMC activity and GMFCS level.

2.3.4.2. Task-evoked prefrontal cortex activity in CP

The earliest fNIRS investigation of prefrontal cortex (PFC) activity in CP reported similar temporal patterns of hemodynamic activity in 2 adults with BCP as neurotypical individuals during a ball-grasp and drop task (352). However, PFC laterality differed between the groups, with both individuals with BCP exhibiting ipsilateral PFC dominance, in contrast to the bilateral-to-

contralateral PFC dominance observed in the neurotypical group. In children with UCP, no hemispheric difference in PFC activity was noted during a shape-matching task (57), although overall PFC activity was greater than controls. Group differences were more pronounced with the more affected arm, increasing task difficulty (57), and during dual-task conditions with a dynamic postural challenge of ball-sitting (58). Greater PFC activity during the dual-task was also linked to greater dual-task cost in children with UCP. Following intensive CIMT (59), reduced PFC activity in children with UCP was comparable to baseline levels in controls, but links between PFC activity and functional improvements were not reported.

Recent fNIRS studies assessing PFC activity during whole-body tasks such as robot-assisted gait training (56) and functional strength (progressive lateral step-up) test (135) revealed task-dependent patterns. Perpetuini et al. (56) reported contrasting changes in PFC activity across hemispheres, but no significant changes in SMC activity following robot-assisted gait training in children with BCP. Cortical activity changes were evident only at the end of the 4-week intervention, suggesting a dose-dependent neuroplastic response in children with more severe gross motor impairment. Licea et. al. (135) observed suppressed PFC activity in children with CP compared to matched controls across all levels of a progressive lateral step-up test, even after controlling for task performance differences. However, no significant association between PFC activity and step-up task performance was observed in the CP group.

2.3.4.3. Resting-state functional connectivity in CP

Three fNIRS studies assessed resting-state functional connectivity in CP (43, 351, 353). Cao et al. (43) noted lower frequency of functional connections in the pre-, supplementary and primary motor cortices in children with UCP following intensive CIMT, which was linked to improved functional outcomes. However, changes were observed only in those with mild-moderate manual ability impairment (MACS level II, no change in those at MACS level I) and were not sustained at 6 months. More recent studies (351, 353) reported similar reductions in intra- and inter-hemispheric functional connectivity in the PFC and SMC of children with CP at rest, during

assisted arm-cycling (351) and passive leg bicycling (353). Decreased inter-hemispheric SMC connectivity in UCP was also strongly related to worse gross motor ability (higher GMFCS level). Zhang et al. (351) reported greater resting-state activity in the dominant SMC which remained unchanged during passive-assisted arm cycling, unlike the increased activity observed in controls. More advanced network analyses by Xie et al (353) also revealed decreased global and local neural network efficiency in individuals with CP both at rest and during passive bicycling, alongside decreased strength of motor-prefrontal connections from the non-dominant motor cortex.

2.4. Discussion

2.4.1. Settings and sample characteristics

Most studies included in this review arose from research conducted over the past 15 years, with nearly all originating from North America. No studies from low- or middle-income countries were identified, despite these regions accounting for up to 98% of the global caseload of CP in children under 5 years (354) with significantly higher CP-related morbidity (74). These constrained study settings reflect equity challenges in fNIRS research (332), which also presents researchers with opportunities to explore collaborations with not-for-profit organizations (e.g., Bill and Melinda Gates Foundation's Brain Imaging for Global Health (BRIGHT) Project (355, 356)) and communities in more diverse settings (209). The low-cost and portability of fNIRS make it a particularly promising neuroimaging modality for use in these underserved regions.

Despite small sample sizes (range = 2-24; median = 8), individuals with CP across a wide age range (3-42 y), different topographies (UCP, BCP) and varying levels of functional impairment (GMFCS, MACS levels) were assessed, broadly supporting the feasibility of fNIRS use in CP. Spastic CP was most frequently reported sub-type across studies, with dystonia reported in two studies (45, 48). Notably, no study included subjects with the less common dyskinetic or ataxic sub-types of CP, despite their distinct clinical phenotype (76) and evidence of altered neural connectivity (357, 358). None of the studies were pre-registered (359), and only one study reported

a priori power analyses for sample size estimation (58), possibly reflecting the incipient nature of the field. Adequate powering of neuroimaging-focused studies to detect interventional neuroplasticity in CP is an important issue, with specific sample size recommendations proposed for some MRI-based outcomes (360). While similar guidelines for fNIRS studies are currently lacking (but see (359) for general discussion), future fNIRS research should consider adopting standardized experimental protocols (361), consistent preprocessing pipelines (362), and engaging in collaborative initiatives such as the ManyBabies 3 NIRS project (363) to facilitate data pooling across studies.

Additionally, only 10 individuals with significant gross motor impairment (GMFCS levels IV, V; ~6% of total participants with CP) were assessed across two studies (56, 353), despite this group comprising close to 30% of all individuals with CP (364). This underrepresentation highlights ongoing equity challenges in neuroimaging research in CP, restricting generalizability of findings and marginalizing individuals already less likely to access and benefit from evidence-based interventions (365). A similar issue was observed for upper limb assessments in individuals with UCP, with only four individuals classified at MACS level IV or V included across two studies (57, 59), while MACS levels were not reported in three of 11 studies using upper limb tasks (44, 351, 352). As fNIRS outcomes can vary across functional abilities on both the GMFCS and MACS (47), future fNIRS studies in individuals with CP should include these descriptors to improve generalizability of findings and facilitate aggregation of results.

2.4.2 Experimental protocols

Most studies incorporated tasks that were either functional (e.g., shape-matching, seated cycling, walking) or resembled real-world behavior (e.g., simulated pouring). Only 3 studies incorporated whole-body tasks (46, 56, 135), and upper limb tasks were performed in seated or reclined positions that may not reflect real-world behavior. Two studies employed experimental protocols with movements that were either fully passive (353) or active-assisted (351). Functional MRI work in UCP demonstrated that passive movements evoke lower cortical activation than self-

generated active movements (366), and passive modalities do not reflect the task-focused, child-driven and activity-based principles of evidence-based best practices for CP neurorehabilitation (367). While the great potential of fNIRS to assess neurophysiology during real-world tasks in unconstrained environments remains largely untapped (201), recent efforts to integrate more functional assessment protocols such as robot-assisted walking (56) and a progressive lateral step-up test (135) are promising, and may guide future fNIRS research in CP.

2.4.3. Sensorimotor cortex activity: (A) Unilateral cerebral palsy

Most fNIRS studies in UCP reported exaggerated SMC activity, with potential contributors including mirror movements (42), lower functional abilities (higher MACS levels) (47), greater task complexity (asymmetric versus symmetric bimanual or unimanual tasks) (47), and deficits in upper limb selective voluntary motor control (45). Functional MRI studies in UCP reported similar heightened SMC activity during impaired hand movement (164, 366), including increased bilateral (366) and ipsilateral (contralesional) SMC activity (164), with the latter related to residual hand function and strength of mirror movements (164). Mirror movements may reflect altered neurophysiology due to early developmental injury in UCP (368), and may have potential clinical implications such as reduced bimanual function (369, 370). Despite early fNIRS work suggesting mirror movements contribute to increased SMC activation in UCP (42), their presence and impact was inconsistently reported. Future studies should report clinically observable mirror movements, with quantitative tools available for more detailed analyses (371).

Studies assessing hemispheric lateralization of SMC activity in UCP reported age-related variability (41), bilateral activation (43) or trends of ipsilesional SMC dominance during unimanual (47) and bimanual tasks (45). The functional relevance of SMC lateralization in UCP was less studied, although contralesional SMC dominance during asymmetric bimanual squeezing was related to better daily function (45), while SMC activity during non-dominant hand squeezing and ankle dorsiflexion was not related to functional outcomes (47). Variability in activation patterns reflects methodological differences across studies and aligns with functional MRI literature in UCP

that describes three main lateralization patterns (163): bilateral dominance in motor functions, ipsilesional dominance in somatosensory functions, and contralesional dominance in language functions. Ipsilesional SMC activation involves the recruitment of preserved perilesional tissue, and generally correlates with better clinical outcomes in UCP (160) and stroke (372).

The diverse SMC lateralization patterns reflect the nuanced dynamics of cortical activation in UCP, a complexity further highlighted by intervention studies. The sole fNIRS study reporting SMC changes post-intervention found increased contralesional SMC dominance in UCP immediately after CIMT (43) that declined at 6 months and was related to worse bimanual function (43). A review of interventional neuroplasticity reported increased ipsilesional SMC activity as the most common change observed post-intervention in UCP (321). Conversely, a recent functional MRI study reported increased ipsilesional and decreased contralesional SMC activity after hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) intervention, with better clinical outcomes related to reduced brain activity (373). Lateralization of SMC activity in UCP reflects adaptive developmental processes after early developmental injury (see (96) and (137) for detailed review) that vary by lesion size (144) and timing (140). Large lesions may prevent ipsilesional SMC control, rendering contralesional activity the sole contributor to motor function (159). Laterality also varies by side tested and fatigue (374). A multimodal neuroimaging study highlighted unique neurophysiological patterns across individuals with UCP (157), emphasizing significant individual variability and highlighting the challenge of defining clear neural structure-function relationships in this population.

2.4.3. Sensorimotor cortex activity: (B) Bilateral cerebral palsy

While limited, fNIRS studies in BCP offer valuable insights into this group's distinct neurophysiology. Increased SMC and superior parietal lobule activity during treadmill walking in an exploratory study in children with BCP (46) mirrors the excessive motor and parietal cortex activation observed in a larger EEG gait study in UCP (174). Similar to fNIRS reports in UCP (47), greater SMC activation in BCP was related to lower functional abilities (higher GMFCS levels)

(47), worse selective motor control, and lower PEDI-CAT mobility scores (48). However, unlike UCP, where greater SMC activation is seen during non-dominant hand squeezing than ankle dorsiflexion, the BCP cohort demonstrated similar SMC activity across these tasks (47), potentially indicating more severe upper extremity involvement in this group (120). This is supported by EEG evidence of exaggerated dominant SMC activation in BCP during reaching (375, 376) that was also associated with slower, less efficient movements and poor dexterity, suggesting SMC over-recruitment may reflect excessive cortical resource use during arm movements in BCP (375).

Hemispheric lateralization of SMC activity in BCP was task-dependent, with ipsilateral SMC dominance during non-dominant ankle dorsiflexion (48) and contralateral dominance during non-dominant hip movements, cycling (48) and hand squeezing (47). This pattern contrasts with the bilateral activation commonly noted in UCP, where underlying brain lesions are often focal, well-defined, and distinctly impacted by the timing and location of insult, such as in perinatal stroke (97). The more widespread bilateral brain injury in BCP results in more severe motor impairments and higher incidences of comorbidities such as intellectual and visual impairments (377), that further complicates task performance during neuroimaging studies. Reorganization following bilateral lesions likely follows different developmental patterns than those seen after unilateral injuries, due to the absence of a relatively intact hemisphere that can act as a scaffold to support adaptive plasticity (377). A recent functional MRI study in mildly impaired children with BCP (378) reported contralateral SMC dominance during non-dominant ankle dorsiflexion, although a shift to greater ipsilateral dominance and lower activation volume post-intervention were independently associated with motor skill gains. These observations highlight the potential for targeted interventions to influence cortical reorganization and improve motor outcomes in BCP. However, the scarcity of functional neuroimaging studies in BCP is a significant barrier to understanding the complexity and variability of neural structure-function relationships in this group. Mobile neuroimaging tools such as fNIRS, with their methodological flexibility and resilience to motion artifacts, are well-suited to addressing this research gap.

2.4.4. Prefrontal cortex activity

Greater PFC activity in UCP during a shape-matching task scaled with increased task difficulty, non-dominant arm use (57), and concurrent postural challenge (58). After CIMT intervention, PFC activity in CP attenuated to levels comparable to controls (59), but no link to improved functional outcomes was reported, generating doubt on whether attenuated PFC activity reflected "normalization" of cortical activity or was the byproduct of generalized motor skill acquisition. The PFC is a prime target for interrogation by fNIRS due to its accessible location underneath the hairless forehead region, allowing for optimal signal acquisition (379). Although the PFC is not involved in motor execution, it mediates executive functions such as working memory, sustained attention and action planning that support and enable motor planning and prediction (52, 53). Exaggerated PFC activity during motor tasks may represent a resources allocation strategy (298) for enhanced motor planning in UCP (380). In contrast, children with BCP with greater motor involvement displayed more variable PFC activity patterns after robot-assisted gait training (56), although the small, heterogenous sample and absence of a control group limits definitive conclusions on the functional impact of these changes.

The variability in PFC activity changes following different motor interventions highlights a need for further investigation into the neural correlates of cognitive deficits and their impact on motor outcomes in CP. Half of all children with CP are estimated to display concurrent intellectual disability (115), with a recent meta-analysis identifying moderate-large deficits across all executive function domains in individuals with CP, regardless of gross motor or manual ability (GFMCS and MACS levels, respectively) (381). Given the intimate linkage of cognitive and motor development (382) and their combined relation to the PFC (383), cognitive deficits in CP significantly impacts their ability to navigate real-world tasks that involve dual-tasking (384, 385). A recent MEG study in adults with CP (386) reported weaker PFC oscillatory activity during the encoding phase of working memory was related to worse cognitive outcomes and lower gross motor function (higher

GMFCS levels). Despite the potential for fNIRS to assess PFC activity during ecologically valid tasks in real-world settings, fNIRS studies assessing PFC activity during cognitive tasks or during physical activity are lacking (387). Notably, the sole fNIRS study to incorporate a physically demanding task reported suppressed PFC activity in children with CP during a progressive lateral step-up test (135) which was maintained after controlling for their lower performance. However, the lack of significant associations between FPC activity and step-up performance in CP suggests factors such as lower exercise tolerance or psychological factors such as impaired attention and emotional dysregulation may contribute to the suppressed PFC activity patterns observed in this group. These novel observations emphasize the need for future fNIRS research to explore how PFC activity impacts cognitive-motor interactions in CP.

2.4.5 Functional connectivity and cortical networks

Early fNIRS-based functional connectivity research (43) revealed greater frequency of connections between the supplementary motor, premotor, and primary motor cortices in children with UCP, with most connections observed from the supplementary motor area, although connection strength was not quantified. Conversely, recent fNIRS studies (351, 353) reported lower intra- and inter-hemispheric resting-state functional connectivity in the PFC and SMC of children with UCP, with attenuated connectivity maintained during assisted arm (351) and passive leg cycling (353), and related to lower gross motor function. Reduced functional connectivity across the sensory and motor areas was also widely reported in the functional MRI literature in UCP (183), although intra-hemispheric connectivity in these regions may vary by pattern of corticospinal tract wiring (388). Lower efficiency of both global and local cortical networks in UCP reported in a recent fNIRS study (353) mirrored observations from studies using structural MRI (389) and diffuse tensor imaging (390) reporting similar lowered global efficiency in children with BCP.

Notably, fNIRS functional connectivity research did not include studies in individuals with BCP, in whom functional MRI revealed widely varying patterns of functional connectivity across cortical regions. Significantly widened and increased connections reported with functional MRI in

BCP between the somatosensory cortices (391), SMC and supplementary motor areas (392), contrasts against decreased connectivity in the bilateral SMC and parietal cortices. (130, 358). Functional connectivity analyses has also been used to examine neural networks mediating non-motor functions, with evidence of altered networks in CP extending to domains of language (324), visuomotor function (393) and cognition (323). These domains represent rich avenues for future research, with recent development of wearable, high-density fNIRS devices (394) setting the stage for fNIRS investigation of these unexplored topics in CP.

2.4.6. fNIRS methodologies

While fNIRS is a promising tool for real-world neuroimaging, its outcomes are susceptible to subjective researcher decisions (395) on issues of signal quality assessment (379, 396, 397), data processing pipelines (398, 399), and statistical analyses methods (400). Concerns about potential data misreporting have spurred a movement toward greater transparency in decision-making and reporting within the fNIRS community, with calls for pre-registration of study protocols and analyses decision-making algorithms (359) to mitigate publication bias and false positive results (211, 401). While assessing methodological rigor and modality-specific challenges of fNIRS exceeds the scope of this review (see (402) for comprehensive recommendations), we provide a detailed summary and critical appraisal of fNIRS methods in **Table 2.S8**. Further, as fNIRS shares neurovascular underpinnings (BOLD response) with functional MRI, readers are referred to Reid et al.'s excellent review (166) for a detailed examination of challenges in interpreting activation changes in functional neuroimaging.

2.5. Limitations

This review aimed to inform future research by synthesizing peer-reviewed empirical literature on the application of fNIRS in CP and excluded grey literature and non-scientific articles. While this approach is consistent with other scoping reviews (347, 403, 404), it may have resulted in the omission of additional experimental settings and observations. However, we provide readers

with a list of relevant doctoral dissertations and theses obtained through a systematic search (**Table 2.S2**). The inclusion of studies with small sample sizes and methodological limitations (e.g., Chaudhary et al.'s pilot study on 2 adults with CP (352)) was necessitated by the nature of scoping reviews. Quality appraisal analyses were performed to address concerns about potential bias, though we acknowledge that caution is warranted when interpreting the study results. Finally, the diversity of fNIRS outcomes across studies prevented aggregation and quantification via meta-analyses, underscoring the need for standardized experimental protocols for easier data pooling and comparisons across studies (183). Despite these limitations, this review provides a comprehensive overview on the use of fNIRS in CP that can inform future investigations in this field.

2.6. Challenges with fNIRS use in CP

Despite its advantages as a user-friendly, motion-resistant and cost-effective functional neuroimaging modality, fNIRS remains underutilized in CP neuroimaging research, with only 16 studies identified in this review. Alongside aforementioned limitations such as poor imaging depth, inability to image deeper brain structures, systemic contamination, and data collection challenges with darker skin tones or thick hair, other potential barriers also require recognition. A lack of research confirming fNIRS reliability in CP undermines confidence in its ability to track intervention effects on cortical function. Recruitment and compliance issues are frequent, with early studies that used wired systems reporting high attrition rates (10-33%) and exclusion of data (20% in one study (45)) due to cortical lesions in brain regions of interest. Practical challenges include prolonged setup times, resistance to fNIRS caps from sensory hypersensitivity, and participant discomfort, compounded by the lower signal-to-noise ratio of fNIRS than functional MRI, necessitating longer and more frequent trials (40). The physiological underpinnings of fNIRS also present challenges in CP. Neurovascular coupling, the basis of fNIRS measurements, may be altered in CP due to brain injuries such as periventricular leukomalacia or perinatal stroke (405), which impair vascular autoregulation (216) and integrity (217). This disrupts hemodynamic signals

and complicates interpretation of cortical activity(218). Additionally, historical reliance on conventional neuroimaging modalities such as functional MRI and EEG, coupled with limited awareness of recent advances in fNIRS technology, has slowed the adoption of fNIRS in CP research.

However, rapid improvements in fNIRS hardware and software offers solutions to many of these challenges (406). Recent innovations such as infant-friendly dual-tip optodes (407), scalable modules for high-density whole-head imaging in infants (408) and customizable optode attachments have significantly improve feasibility. Implementing standardized fNIRS methodologies (49), analyses pipelines (362, 409), and reporting guidelines (402) can further enhance reliability and reproducibility. Targeted efforts to establish fNIRS reliability in CP and adapt this technology for neurodiverse populations could significantly expand its utility in understanding neurophysiology and intervention effects in CP.

2.7. Future directions

The exponential rise in fNIRS studies in neurodevelopmental disorders and neurodivergent populations (189, 192-194, 410, 411) reflects the growing recognition of fNIRS as a valuable tool for investigating brain function in neurodivergent populations for whom conventional neuroimaging is challenging (412). Rapid technical, methodological and technological developments in fNIRS have propelled the field beyond initial feasibility assessments (413-415) towards the identification of diagnostic and prognostic biomarkers ("fNIRS signatures" (190)) of significant translational value to clinicians and researchers. Future research avenues for exploration include the integration of fNIRS with other neuroimaging modalities such as functional MRI (416), EEG (417), MEG (418, 419), and transcranial magnetic stimulation (420, 421), to provide real-time feedback of functional performance and progress during rehabilitation (422). This multimodal approach may also uncover underlying pathophysiology (157, 165, 166) and enhance confidence in reported results by reducing bias, and minimizing signal noise (332). Hyperscanning protocols

that enable synchronous assessment of multiple individuals in naturalistic settings are particularly well-suited for fNIRS, and hold promise for studying parent-child interactions (423). This innovative approach may shed light on the neurophysiological underpinnings of impaired inter-personal social interactions in CP (203), and promote family-centered care by facilitating parental involvement in therapy (204). Additionally, the integration of fNIRS into brain-computer interface applications (205), either alone or in conjunction with other modalities such as EEG (417, 424), may offer tangible benefits to individuals with CP who experience severe motor, language, or cognitive impairments (206).

The overarching goal of translational fNIRS research is to integrate fNIRS into clinical settings for individualized assessment, prognosis and monitoring of treatment fidelity and effectiveness in clinical populations of all ages and functional profiles. Achieving these goals in the context of CP requires (1) continuous advances in fNIRS hardware and software, (2) transparent and comprehensive reporting of experimental methods and results, (3 collaboration between funding agencies, industry, researchers and community partners, and most importantly, (4) sustained involvement of individuals with lived experience and their families, who stand to benefit most from this research. This review comprehensively summarizes the current state of fNIRS research in CP and represents a critical first step towards realizing these ambitious objectives.

2.8. Conclusion

This review analyzed 16 studies that confirmed the feasibility and utility of fNIRS for evaluating cortical activity, functional connectivity, and neuroplasticity in individuals with CP, with exaggerated sensorimotor cortex activity observed across motor tasks alongside task-dependent PFC activity patterns. While fNIRS demonstrated utility in capturing neuroplastic changes post-intervention, the lack of reliability data undermines confidence in its application in interventional research. While most studies demonstrated moderate-strong methodological quality, specific challenges to fNIRS use were identified, with recommendations for enhanced rigor and

transparency outlined. Leveraging recent technical advancements may help address these challenges and transition fNIRS research beyond feasibility toward integration into clinical practice. By enabling individualized assessments and real-time monitoring, and facilitating family-centered care through improved neurophysiological understanding of parent-child interactions, fNIRS offers transformative potential for CP research and rehabilitation that remains largely untapped.

Table 2.S1: Systematic search strategy used for the PubMed database

Search Number	Search query	*Records retrieved
1	"cerebral palsy"[MeSH] OR "stroke/congenital"[MeSH]	24561
2	"cerebral pals*"[Title/Abstract] OR "perinatal stroke"[Title/Abstract:~2] OR "neonatal stroke"[Title/Abstract:~2] OR "Little disease"[Title/Abstract] OR "spastic dipleg*"[Title/Abstract] OR "spastic hemipleg*"[Title/Abstract]	30784
3	#1 OR #2	34982
4	"spectroscopy, near-infrared"[MeSH]	16714
5	NIR [Title/Abstract] OR NIRS [Title/Abstract] OR fNIR*[Title/Abstract] OR "functional near-infrared spectroscop*"[Title/Abstract] OR "near-infrared spectroscopy"[Title/Abstract] OR "near infrared spectroscopy"[Title/Abstract] OR "optical imag*"[Title/Abstract]	60332
6	#4 OR #5	63796
7	"magnetic resonance imaging"[MeSH] OR "magnetic resonance spectroscopy" [MeSH]	765568
8	#6 NOT #7	61280
9	Brain[Title/Abstract] OR Cerebral[Title/Abstract] OR Cortical[Title/Abstract] OR Neural[Title/Abstract] OR Neuron*[Title/Abstract] OR Hemodynamic*[Title/Abstract] OR haemodynamic*[Title/Abstract] OR Prefrontal[Title/Abstract] OR Sensor*[Title/Abstract] OR Motor*[Title/Abstract] OR Cortex[Title/Abstract] OR Cortices[Title/Abstract] OR area*[Title/Abstract] OR region*[Title/Abstract]	6209604
10	Correlate*[Title/Abstract] OR activ*[Title/Abstract] OR response*[Title/Abstract] OR function*[Title/Abstract] OR plasticity[Title/Abstract] OR organization[Title/Abstract] OR reorganization[Title/Abstract] OR neuroplastic*[Title/Abstract] OR connectiv*[Title/Abstract] OR network*[Title/Abstract]	12418564
11	#9 AND #10	3071107
12	#3 AND #8 AND #11	31

*As of July 18, 2024**; Bolded** items indicate nested search 'sets'

Table 2.S2: Relevant grey literature from ProQuest database search and hand-searching

Author (Year)	Title of Dissertation / Thesis	Reference
Asanani, N (2008)	Study of NIRS based motor cortex activation patterns in cerebral palsy affected kids using image based metrics	(425)
Parlapalli, R. (2008)	Comparison of hemodynamic response non-linearity using simultaneous near infrared spectroscopy and magnetic resonance imaging modalities	(426)
Dhamne, S. (2009)	Diffuse optical imaging of brain function under repetitive transcranial magnetic stimulation and in children with cerebral palsy	(427)
Khan, B. (2009)	Functional near infrared spectroscopy for the assessment of motor cortex plasticity in pediatric subjects affected by cerebral palsy	(428)
MacGregor, R. (2009)	Effects of specifically sequenced massage on spastic muscle properties and motor skills in adolescents with cerebral palsy	(429)
Chaudhary, U (2013)	Functional near infrared spectroscopy study of language, joint attention and motor skills	(430)
Hervey, N. (2014)	A GLM/ICA analysis using motion tracking and electromyography differentiates between brain activation due to intended and unintended motions in fNIRS images acquired during a finger tapping task performed by children with cerebral palsy	(431)
Surkar, S. (2016)	Identification and intervention for action planning deficits in children with hemiparetic cerebral palsy	(432)
Cao, J. (2017)	Revealing Hemodynamic Response and Dynamic Changes in Functional Cortical Networks Using Functional Near-Infrared Spectroscopy (FNIRS)	(433)
Licea, J. (2023)	Interrelationships among brain, muscle and physical activity in children with cerebral palsy	(434)

Table 2.S3: Modified Downs and Black checklist for methodological quality assessment

ITEMS	Yes	Unable to determine	No
Validity			
1. Is the hypothesis/aim/objective of the study clearly described?	☐		☐
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	☐		☐
3. Are the characteristics of the subjects included in the study clearly described?	☐		☐
5. Are the distributions of principle confounders in each group of subjects to be compared clearly described?	☐	☐ **partially**	☐
6. Are the main findings of the study clearly described?	☐		☐
7. Does the study provide estimates of the random variability in the data for the main outcomes?	☐		☐
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	☐		☐
External validity			
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	☐	☐	☐
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	☐	☐	☐
Internal validity (selection bias)			
16. If any of the results were based on data dredging, was this made clear?	☐	☐	☐
18. Were the statistical tests used to assess the main outcomes appropriate?	☐	☐	☐
20. Were the main outcome measures used accurate (valid and reliable)?	☐	☐	☐
Internal validity (confounding)			
21. Were study subjects recruited from the same population?	☐	☐	☐
22. Were study subjects recruited over the same period of time?	☐	☐	☐
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	☐	☐	☐

Table 2.S4: Methodological quality scores based on the modified Downs and Black checklist

Author (Year)[Ref]	Reporting							External Validity		Internal Validity (Selection bias)			Internal Validity (Confounding)			Total (/15)	Score %
Checklist Question	1	2	3	5*	6	7	10	11	12	16	18	20	21	22	25		
Khan (2010) [44]	1	1	1	0.5	1	1	1	0	0	1	1	1	0	1	1	11.5	76.7
Tian (2010)[41]	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	13	86.7
Hervey (2014)[42]	1	1	1	1	1	0	0	0	0	1	1	1	0	0	1	9	60.0
Cao (2015)[43]	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	11	73.3
Chaudhary (2014)[352]	1	1	0	1	1	0	0	0	0	1	1	1	0	0	1	8	53.3
Kurz (2014)[46]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	13	86.7
Sukal-Moulton (2018)[48]	1	1	1	1	1	1	1	1#	0	1	1	1	1#	1#	1	14	93.3
de Campos (2020)[45]	1	1	1	1	1	1	1	1#	0	1	1	1	1#	1#	1	14	93.3
Sukal-Moulton (2020)[47]	1	1	1	1	1	1	1	1#	0	1	1	1	1#	1#	1	14	93.3
Surkar (2018)[57]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	100.0
Surkar (2018)[59]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	14	93.3
Surkar (2021)[58]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14	93.3
Perpetuini (2022)[56]	1	1	1	1#	1	1	1	1	1	1	1	1	0	1	0	13	86.7
Zhang & Xu (2023)[351]	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	11	73.3
Xie (2024)[353]	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	13	86.7
Licea & Khan (2024)[135]	1	1	1	1	1	1	1	1#	1#	1	1	1	1#	1#	1	15	100
Item Total	16	16	15	15.5	16	14	13	11	7	16	16	16	9	8	14		**Mean % Score**
Item Percentage	100%	100%	94%	97%	100%	88%	81%	69%	44%	100%	100%	100%	56%	50%	88%		**84.4**

*Partial score permitted; #Information provided on request from study authors

Table 2.S5: Study background and sample characteristics

First Author (Year)[Ref]	Setting	Design	Sample characteristics and functional classification	Structural brain scan and brain pathology (number of subjects)	Power analyses
Khan (2010) [44]	Texas, USA	Observational case-control; dual-timepoint (8weeks apart for fNIRS repeatability)	**4 UCP** (2 Male; 5 recruited, 1 lost to follow-up, 20% drop-out; MACS classification NR; Mirror movement: NR) 4 TD (3 Male; 5 recruited, 1 lost to follow-up)	sMRI confirmed single unilateral subcortical lesion	Post-hoc sensitivity [power (1-ß)]
Tian (2010)[41]	Texas, USA	Observational case-control; dual-timepoint (days-2weeks apart for fNIRS repeatability)	**10 UCP** (4 Male; 15 recruited, 5 lost to poor signal (4 dark hair,1 body motion), 33% data loss; MACS classification I-II*; Mirror movement: Assessed as mild in tested hand) ^7 TD (3 Male)*^16y TD analyzed separately; *Specific inclusion criterion, subject-wise NR*	sMRI confirmed single unilateral subcortical lesion	NR
Hervey (2014)[42]	Texas, USA	Observational cross-sectional; single-timepoint	**4 UCP** (Male NR; 8 recruited, 3 excluded (no mirror movements), 1 poor compliance and motion, 13% drop-out; MACS classification: 1 level I, 3 level II; Mirror movement: Specific focus of study, assessed as present/absent in each hand) 8 TD (5 Male)	sMRI available but pathology NR$ $*One subject with right peri-insular hemispherectomy and right-sided midline shift*	NR
Cao (2015)[43]	Texas, USA	Interventional case-control; Longitudinal assessment - baseline, post-intervention (2wk), follow-up (6mo)	**6 UCP** (4 Male; drop-out NR; MACS classification: 2 level I, 4 level II; Mirror movement: NR) 5 TD (3 Male)	sMRI confirmed single unilateral cortical/subcortical lesion affecting motor area	Post-hoc sensitivity [power (1-ß)]
Chaudhary (2014)[352]	Florida, USA	Observational cross-sectional pilot; single timepoint	**2 spastic BCP** (2 Males; drop-out NR; MACS classification NR, GMFCS classification NR (wheelchair-users); Mirror movement: NR) 7 TD (Males: NR)	NR	NR
Kurz (2014)[46]	Nebraska, USA	Observational cross-sectional; single timepoint	**4 spastic BCP** (2 Male; drop-out NR; GMFCS classification: 3 level II, 1 level III; Mirror movement: NR) 8 TD (1 Male)	sMRI implied*, all with periventricular leukomalacia *Exclusion if large space-occupying lesion and/or cortical volume loss	NR
Sukal-Moulton (2018)[48]	NIH Maryland, USA	Observational cross-sectional; single-timepoint	**14 spastic BCP** (dystonia in 10/14) (5 Male; drop-out NR; GMFCS classification: 4 level I, 7 level II, 3 level III; Mirror movement: Quantified with sEMG cross-correlation during task) 14 TD (9 Male)	sMRI confirmed periventricular leukomalacia (12), corpus callosum agenesis (1), encephalitis with typical MRI (1)	NR
de Campos (2020)[45]	NIH Maryland, USA	Observational case-control; single timepoint	**8 spastic UCP** (dystonia in all) (2 Male; 10 recruited, 2 removed post-hoc due to large cortical lesions in region of interest on MRI, 20% drop-out; MACS classification: 2 level I, 6 level II; GMFCS classification: 3 level I, 5 level II; Mirror movement: NR) 9 TD (2 Male)	sMRI confirmed prenatal stroke (4), peri/neonatal stroke (2), post-infancy stroke (2)	NR

Sukal-Moulton (2020)[47]	NIH Maryland, USA	Observational cross-sectional; single-timepoint	**10 spastic UCP** (2 Male) **14 BCP** (5 Male) (Drop-out NR; MACS classification: 8 level I (all BCP), 14 level II, 3 level III (all UCP); GMFCS classification: 8 level I, 12 level II, 4 level III; Mirror movement: Assessed visually (video) in each limb as mild (present < 50%) or strong (>50%) 16 TD (9 Male)	sMRI available but pathology NR	NR
Surkar (2018)[57]	Nebraska, USA	Observational cross-sectional; single timepoint	**12 UCP** (7 Male; drop-out NR; MACS classification: 2 level II, 8 level III, 2 level IV; Mirror movement: NR) 15 TD (8 Male)	sMRI implied* with perinatal stroke (6), neonatal stroke (4), periventricular leukomalacia (1), schizencephaly (1) *Exclusion if frontal cortical lesions	NR
Surkar (2018)[59]	Nebraska, USA	Non-randomized intervention, dual-timepoint (baseline, post-intervention (2week))	**9 UCP** (4 Male; 9 recruited, 1 1 did not complete post-intervention fNIRS, 10% drop-out; MACS classification: 2 level II, 8 level III, 1 level IV, 1 level V; Mirror movement: NR) 15 TD (8 Male)	sMRI implied* with perinatal stroke (7), periventricular leukomalacia (1), schizencephaly (1) *Exclusion if frontal cortical lesions	NR
Surkar (2021)[58]	Nebraska, USA	Observational cross-sectional; single-timepoint	**9 UCP** (5 Male; drop-out NR; MACS classification: 1 level I, 1 level II, 7 level III; Mirror movement: NR) 12 TD (7 Male)	sMRI implied* but pathology NR *Exclusion if frontal cortical lesions	Performed *a priori*
Perpetuini (2022)[56]	Foggia, Italy	Non-randomized single group intervention; Three timepoint assessment (baseline, mid-(2wk), and post-intervention (4wk))	**7 spastic BCP** **1 spastic UCP** (Males 5#; 10 recruited, 2 lost due to COVID-19, 20% drop-out; GMFCS classification: 1 level I, 1 level III, 5 level IV, 1 level V; Mirror movement: NR) No TD included *#Sex of CP on request from authors*	sMRI NR; #hypoxic-ischemic encephalopathy (7), hemorrhagic encephalopathy (1) #Provided on request from study authors	NR
Zhang & Xu (2023)[351]	Beijing, China	Observational cross-sectional; single-timepoint	◆**15 UCP** (9 Male; drop-out NR; GMFCS classification: 1 level I, 3 level II, 4 level III, 7 level IV; Mirror movement: NR) 21 TD (11 Male) *◆Type of CP not specified, UCP assumed from mention of 'affected side' in fNIRS preprocessing*	NR	NR
Xie (2024)[353]	Beijing, China	Observational cross-sectional; single-timepoint	◆**15 spastic UCP** (9 Male; drop-out NR; GMFCS classification: 1 level I, 4 level II, 5 level III, 5 level IV; Mirror movement: NR) 17 TD (9 Male) *◆Type of CP not specified, UCP assumed from mention of 'affected side'*	NR	NR
Licea & Khan (2024)[135]	Georgia, USA	Observational cross-sectional; single-timepoint	◇**14 spastic CP** (8 Male; drop-out NR; GMFCS classification: all level I; Mirror movement: NR) 14 TD (8 Male) *◇Type of CP not specified; UCP (12) and BCP (2) on request from authors.*	NR	NR

Abbreviations: BCP, Bilateral cerebral palsy; GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; NR: Not reported; sEMG, Surface electromyography; sMRI, Structural magnetic resonance imaging; TD, Typically developing control; UCP, Unilateral cerebral palsy.

Table 2.S6: Experimental procedures

First Author (Year)[Ref]	Limb(s) tested	Region of Interest	Task Design	Task Outcomes
Khan (2010) [44]	Bilateral upper limbs	Bilateral motor cortices	Seated participant performed unimanual, self-paced finger tapping (1-2Hz with visual cues) moving all fingers except thumb on a customized tapping board with wrist strapped.	Quality check via video recording & sEMG to detect unwanted activation/mirror movements on non-tested side
Tian (2010)[41]	Bilateral upper limbs	Bilateral motor cortices	*Same as Khan et al., 2010[63]* except finger tapping frequency fixed (1.5Hz)	*Same as Khan et al., 2010[63]* plus heart rate and peripheral SaO_2 monitored to detect changes in systemic physiology
Hervey (2014)[42]	Bilateral upper limbs	Bilateral motor cortices	*Same as Khan et al., 2010[63]*	*Same as Khan et al., 2010[63]* plus finger kinematics via motion capture markers on each finger
Cao (2015)[43]	Bilateral upper limbs	Bilateral sensorimotor cortices^	*Same as Khan et al., 2010[63]* except finger tapping frequency fixed (1Hz)	NR for finger tapping; CIMT intervention (60hrs) outcomes including Melbourne assessment of upper limb and Assisting Hand Assessment (bimanual function)
Chaudhary (2014)[352]	Dominant upper limb	Bilateral prefrontal cortices	Unimanual ball-throwing/drop task. Standing TD controls grasped and threw the ball into container 4 feet away. Subjects with CP in wheelchair dropped ball into container placed directly below the hand.	NR
Kurz (2014)[46]	Bilateral lower limbs	Bilateral sensorimotor cortices^ and superior parietal lobule	Standing participants performed fixed-paced treadmill walking (0.45m/s) holding handrail, maintaining stable head position with eyes fixed on target at head level	NR
Sukal-Moulton (2018)[48]	Bilateral lower limbs	Bilateral sensorimotor cortices^	Semi-recumbent participants performed multiple tasks (1Hz with audiovisual cues): Non-dominant ankle dorsiflexion and sling-support hip flexion, bilateral ankle dorsiflexion, single-leg and bilateral cycling with zero-resistance cycle.	Muscle activation (sEMG) from bilateral rectus femoris, vastus lateralis, semimembranosus, tibialis anterior, and medial gastrocnemius
de Campos (2020)[45]	Bilateral upper limbs	Bilateral sensorimotor cortices^	Seated participants performed multiple bimanual tasks (0.67-1Hz with audiovisual cues): symmetric (in-phase) squeezing, asymmetric (anti-phase) squeezing, simulated pouring with dominant, non-dominant hand.	Muscle activation (sEMG) for bilateral flexor carpi radialis; Hand kinematics via motion capture marker during simulated pouring;
Sukal-Moulton (2020)[47]	Non-dominant lower and upper limb	Bilateral sensorimotor cortices^	Semi-recumbent participants performed non-dominant hand squeezing (*same as de Campos et al. 2020[45]*) and non-dominant ankle dorsiflexion (*same as Sukal-Moulton et al. 2018[48]*).	Mirror movements via video recording to detect unwanted activation/mirror movements on non-tested side
Surkar (2018)[57]	Bilateral upper limbs	Bilateral prefrontal cortices	Seated participants performed unimanual shape-matching task of varying difficulty (3 levels of task complexity) in random order, with each arm.	Number of shapes matched, task errors, and reaction time from video recordings

Surkar (2018)[59]	Bilateral upper limbs	Bilateral prefrontal cortices	*Same as Surkar et al., 2018[57]*	*Same as Surkar et al., 2018[57]*
Surkar (2021)[58]	Non-dominant upper limb	Bilateral prefrontal cortices	Seated participants performed unimanual shape-matching with varying postural support: Stable chair (single-task) or dynamic ball sitting (dual-task) randomized	Number of shapes matched, reaction time from video recordings, dual task cost
Perpetuini (2022)[56]	Bilateral lower limbs	Bilateral prefrontal, frontal and motor cortices	Participants supported in harness performed assisted walking in a robot-assisted gait trainer (Lokomat)	NR
Zhang & Xu (2023)[351]	Bilateral upper limbs	Bilateral prefrontal and motor cortices	Seated participants performed eye-closed rest, followed by auto-assisted bilateral arm movements on rehabilitative device that switched between active (no assistance) and passive state (assistance provided) based on subject-applied forces.	NR
Xie (2023)[353]	Bilateral lower limbs	Bilateral prefrontal and motor cortices	Seated participants performed eye-closed rest, followed by bilateral passive leg movements on rehabilitative device (Rake MOTOMEDVIVA-2, Germany)	NR
Licea & Khan (2024)[135]	Non-dominant lower limb	Bilateral prefrontal cortices	Standing participant performed a timed lateral step-up test of progressive difficulty (4 levels of increasing step height) with the non-dominant leg as many times as possible in 20seconds	Difficulty-weighted scores per step height accounting for both unassisted and assisted step-ups**;** Composite lateral step-up score

Table 2.S7. Research questions, sample characteristics, and primary findings

Study	Research question(s)	Sample characteristics and task protocol	Primary findings
Khan et al.[96]	1. Can fNIRS-based metrics of unimanual finger tapping-evoked SMC activity differentiate children with UCP from typically developing children?	Four children with UCP (MACS not reported) and four similarly aged, typically developing controls performed unimanual, self-paced finger tapping (1–2Hz)	• 4 of 5 **fNIRS metrics could differentiate UCP from controls;** all reliable across 2 months • **Most sensitive: lower duration/time-to-peak ratio in UCP** • Most specific = lower activation distance-from-midline (more medial) ipsilateral SMC activity in UCP • Similarity concept analysis (fNIRS 'pixels' with similar temporal patterns as primary activation area) can also differentiae UCP from controls
Tian et al.[97]	1. Can 3-dimensional spatiotemporal fNIRS metrics from unimanual finger tapping-evoked SMC activity differentiate children with UCP from typically developing children? 2. Does laterality of SMC activity vary across groups (UCP vs typically developing) and age?	Ten children with UCP (MACS I–II) and eight age-matched typically developing controls performed unimanual, fixed-paced finger tapping (1.5Hz)	• All fNIRS metrics replicable across visits in both UCP and typically developing controls, but **only lower time-to-peak activity in CP different from controls** • **High variability in laterality in UCP** (ipsi-, contra-, and bilateral SMC dominance patterns) • **Overall lower laterality index in UCP** (more ipsi- and bilateral dominance) • **Age effect for laterality in both groups** (more ipsi-bilateral SMC activity in 6-year-old shifting to more contralateral dominance activity after 7 years)
Hervey et al.[98]	1. Can a hybrid fNIRS–sEMG-motion capture analysis identify and isolate contributions of mirror movements to finger tapping-evoked SMC activity in UCP?	Four children with UCP (MACS level I [n = 1] and II [n = 3]) with mirror movements, and eight similarly aged, typically developing controls performed unimanual, self-paced finger tapping (1–2Hz)	• **Synchronously collected motion capture kinematics and sEMG data can identify, isolate and remove mirror movement contribution to bilateral SMC activity in UCP** • Mirror movement contribution captured as increased ipsilateral SMC activity in UCP • Concurrent motion capture with fNIRS may remove contribution of unwanted movements
Cao et al.[99]	1. Are fNIRS-based spatiotemporal metrics of SMC activity, laterality and rest-state functional connectivity sensitive to change immediately and 6 months after an intensive CIMT intervention in UCP? 2. Do fNIRS-based metrics relate to changes in functional outcomes (manual ability) at the same timepoints?	Six children with UCP (MACS I [n = 2] and II [n = 4]) and five similarly aged, typically developing controls performed unimanual, fixed-paced finger tapping (1Hz)	• Post-CIMT **normalization of local hemodynamics in UCP** (increased time-to-peak/duration ratio ≈ controls) **sustained at 6-month** follow-up • Post-CIMT **normalization of SMC laterality in UCP** (increased contralateral dominance ≈ controls) **not sustained at 6-month** follow-up • Post-CIMT **normalization of rest-state functional connectivity in UCP** (lower frequency of connections in UCP ≈ controls) **not sustained at 6-month** follow-up • Clinical improvement post-CIMT only seen in more impaired UCP (MACS level II) • **Laterality normalization** (more contralateral SMC dominance) **post-CIMT may improve unimanual function but worsen bimanual function in UCP**
Chaudhary et al.[100]	1. What are PFC activity patterns during a simple motor task in adults with BCP versus neurotypical adult controls?	Two adults with spastic BCP (MACS, GMFCS not reported, but wheelchair users) and seven neurotypical adult controls performed unimanual ball-grasp and throwing (typically developing controls) or dropping task (CP)	• **Similar temporal pattern of PFC activity in BCP and neurotypical adults** • Contrasting trends of PFC laterality during motor task: ipsilateral PFC dominance in BCP versus bi-contralateral dominance in controls

Kurz et al.[101]	1. Do SMC and superior parietal lobule activity during fixed-speed treadmill walking differ between children with BCP and typically developing children? 2. How does cortical activity relate to variability in temporal parameters of gait?	Four children with spastic BCP (GMFCS II [*n* = 3] and III [*n* = 1]) and eight typically developing controls performed fixed-paced treadmill walking (0.45m/s) holding handrails	• **Greater overall cortical activity in BCP** than controls • **Greater SMC and superior parietal lobule activity in BCP** than controls; no group difference in supplementary motor area activity • **Higher SMC activity related to more variable gait** (stance, stride time) in the combined group
Sukal-Moulton et al.[102]	1. How does magnitude, (spatial) extent, and laterality of SMC activity in BCP differ across lower limb tasks of varying complexity? 2. How does SMC activity relate to clinical outcomes in BCP?	Fourteen children and adults with spastic BCP (GMFCS I [*n* = 4], II [*n* = 7], and III [*n* = 3]) and 14 age-matched neurotypical controls performed unilateral (cycling, non-dominant ankle dorsiflexion and supported hip flexion) and bilateral lower limb tasks (bicycling and bilateral dorsiflexion) in semi-recumbent positions	• **Greater magnitude of SMC activity in BCP** across most tasks; activity **scaled by gross motor ability** (GMFCS level III > level II ≈ level I ≥ controls) • **Greater (spatial) extent of SMC activity in more impaired BCP (GMFCS level III)** during unilateral tasks • **Greater magnitude and extent of SMC activity related to greater muscle activation** across most tasks • Location of maximal SMC activity shifted laterally in BCP for non-dominant ankle dorsiflexion • **Greater magnitude of SMC activity in BCP** during non-dominant ankle dorsiflexion **related to poor lower limb selective motor control, lower walking ability** (ABILOCO) and **lower mobility** (PEDI-CAT) **scores** • Task-dependent variability in SMC laterality in BCP: ipsilateral SMC dominance for distal (ankle) movements, contralateral dominance for proximal (hip) + cycling movements
de Campos et al.[103]	1. How does magnitude, (spatial) extent, and laterality of SMC activity in UCP differ across bimanual tasks of varying complexity? 2. How does SMC activity relate to clinical outcomes in UCP?	Eight children and adults with spastic UCP (MACS level I [*n* = 2] and II [*n* = 6]; GMFCS level I [*n* = 3] and II [*n* = 5]) and nine age-matched neurotypical controls performed bimanual tasks involving ball squeezing (symmetric and asymmetric) and simulated pouring (with each hand)	• **Greater overall SMC activity in UCP** than \ controls across bimanual tasks; **highest activity levels during asymmetric squeezing** • Ipsilesional SMC activity greater than contralesional SMC activity in BCP during each squeezing task • **Greater magnitude of SMC activity during asymmetric squeezing related to higher interlimb muscle co-activation** in UCP (synchronized, or worse task performance) • **Greater contralesional SMC dominance during asymmetric squeezing related to higher daily activity PEDI-CAT scores**
Sukal-Moulton et al.[104]	1. How does magnitude, (spatial) extent, and laterality of SMC activity during distal extremity tasks (hand squeeze, ankle dorsiflexion) differ between individuals with BCP, UCP and typically developing controls? 2. How does SMC activity in CP differ across levels of gross motor function (GMFCS) and manual ability (MACS)?	Ten adolescents and adults with spastic UCP and 14 adolescents and adults with BCP (MACS level I [*n* = 8, all BCP], II [*n* = 14], and III [*n* = 3, all UCP]; GMFCS level I [*n* = 8], II [*n* = 12], and III [*n* = 4]) and 16 similarly aged, typically developing controls performed non-dominant hand squeezing and ankle dorsiflexion in semi-recumbent position	• **Greater SMC activity in both UCP and BCP than controls** across tasks • **Greatest SMC activity during hand squeeze in UCP** (UCP > BCP > controls), **and in those with lower manual ability** (MACS level III (all UCP) > level II > level I (all BCP) > controls) • **Greatest SMC activity during ankle dorsiflexion in BCP** (BCP > UCP > controls), **and in those with lower gross motor function** (GMFCS level III > level II ≈ level I > controls) • **Task-based difference in SMC activity in UCP and controls (squeeze-evoked > dorsiflexion-evoked) not present in BCP** (squeeze-evoked ≈ dorsiflexion-evoked) • **Laterality of SMC activity task-dependent:** (1) hand squeeze: trend for ipsilateral (contralesional) SMC dominance in UCP vs. contralateral dominance in BCP and controls; (2) dorsiflexion: trend for ipsilateral (contralesional) SMC dominance in UCP (lateralization index values: UCP < BCP < controls) • **Greater magnitude and (spatial) extent of SMC activity during (a) hand squeeze related to lower manual abilities** (higher MACS levels), and **(b) dorsiflexion related to lower gross motor function** (higher GMFCS levels)

Surkar et al.[105]	1. How does PFC activity in UCP during a unimanual shape-matching task differ between groups (CP vs typically developing controls) across varying conditions of task complexity?	Twelve children with UCP (MACS level II [*n* = 2], III [*n* = 8], and IV [*n* = 2]) and 15 similarly aged, typically developing controls performed unimanual shape-matching task of varying difficulty, with each arm	• No hemispheric difference in PFC activity • **Greater overall PFC activity in UCP than controls** for task performed with each arm; **differences exaggerated with more-affected arm use** and **scales with task complexity** (hard > moderate > easy) • **Greater PFC activity in combined groups related to prolonged task reaction time and worse manual ability** (fewer blocks on Box-and-Blocks Test, longer Nine Hole Peg test completion time); magnitude of associations scaled with task complexity
Surkar et al.[106]	1. Is PFC activity during unimanual shape-matching in UCP sensitive to change immediately after a Hand-Arm Bimanual Intensive Therapy (HABIT) intervention?	Nine children with UCP (MACS level II [*n* = 2], III [*n* = 8], IV [*n* = 1], and V [*n* = 1]) and 15 age-matched typically developing controls performed unimanual shape-matching task of varying difficulty, with each arm	• **Greater PFC activity in UCP than controls at baseline** for each arm (differences with more affected arm > less affected arm) • **Attenuated PFC activity in UCP post-HABIT intervention** with more-affected arm use that was **not significantly different from baseline PFC activity in controls** • Associations of attenuated PFC activity to improved functional outcomes post-HABIT intervention were not reported
Surkar et al.[107]	1. How does PFC activity during shape-matching in UCP differ from those of typically developing controls across varying conditions of concurrent postural challenge (single-task stable surface sitting vs dual-task dynamic ball-sitting)?	Nine children with UCP (MACS level I [*n* = 1], II [*n* = 1], and III [*n* = 7]) and 12 similarly aged, typically developing controls performed unimanual shape-matching (hard condition of Surkar et al.[105]) with varying postural support: stable chair (single-task) or dynamic ball-sitting (dual-task), order randomized	• **Greater PFC activity in UCP** than controls during each condition (difference during dual-task > single-task) • **Greater PFC activity strongly related to higher dual-task cost in UCP** (*r* = 0.77)
Perpetuini et al.[108]	1. How do SMC and PFC activity patterns in children with CP change during a robot-assisted gait training (RAGT) intervention? 2. Are changes in fNIRS activity patterns in UCP following RAGT related to their motor functions?	Seven children with spastic BCP and one spastic UCP (GMFCS I [*n* = 1], III [*n* = 1], IV [*n* = 5], and V [*n* = 1]) performed harness-supported assisted walking in a robot-assisted gait trainer over 12 sessions (4 weeks)	• Changes in oxy- and deoxyhemoglobin beta values were in the same direction, unlike typically observed anti-correlated patterns • **Postintervention PFC activity levels varied by PFC subregion**: increased orbitofrontal activity bilaterally versus mixed patterns in left dorsolateral PFC activity (increased in Brodmann area 46, decreased in Brodmann area 9) • **Left PFC activity changes used to generate machine-learning estimates of gross motor function** that were **strongly related to measured GMFM-88 scores** (*r* = 0.78) • **Most changes in cortical activity only significant at end of 4-week intervention**, except for left dorsolateral PFC (Brodmann area 46) activation changes observed at 2 weeks
Zhang and Xu[109]	1. How does a single session of assisted bimanual upper limb cycling impact resting-state cortical activity and network connectivity in the primary motor and prefrontal metrics in children with UCP compared with typically developing controls?	Fifteen children with UCP[a] (MACS not reported, GMFCS I [*n* = 1], II [*n* = 3], III [*n* = 4], and IV [*n* = 7]) and 21 age-matched typically developing controls sat eyes-closed at rest, followed by passive-assisted bilateral arm movements on rehabilitative device	• **Greater resting-state activity in contralesional primary motor cortex in CP** than controls • No significant change in cortical activity from rest-to-task or in laterality for CP, unlike increased activity in controls • **Lower inter- and intra-hemispheric connectivity between prefrontal and primary motor cortices at rest and during tasks in CP** • **Decreased interhemispheric connectivity of motor cortices at rest and during task in CP strongly related to lower gross motor ability** (higher GMFCS level) • **Lower resting-state effective connectivity in CP**, with task-evoked increase in connectivity seen only in contralesional primary motor cortex

Xie et al.[110]	1. How does a single session of passive bilateral lower limb cycling impact resting-state cortical activity and network connectivity in the primary motor and prefrontal cortices in children with UCP compared with typically developing controls?	Fifteen children with spastic UCP[a] (GMFCS I [*n* = 1], II [*n* = 4], III [*n* = 5], and IV [*n* = 5]) and 17 age-matched typically developing controls sat eyes-closed at rest, followed by passive bicycling leg movements on rehabilitative device	• **Lower inter- and intra-hemispheric connectivity between prefrontal and primary motor cortices in CP at rest and during passive movement** • **Lower channel clustering and diminishedglobal and local network efficiency between prefrontal and primary motor cortices in CP** at rest and during passive movement • Lower strength of functional connectivity between the bilateral motor cortices, and between the contralesional prefrontal and motor cortices in CP, during passive movement compared with rest • **Decreased interhemispheric connectivity of motor cortices at rest and during passive movement related to lower gross motor ability** (higher GMFCS level) in CP • Lower channel clustering during passive movement also related to lower gross motor ability (GMFCS level)
Licea and Khan[111]	1. How does PFC activity during an incremental test of lower limb functional strength differ between groups (CP vs typically developing children) across progressive increases in task demand (step height)?	Fourteen children with spastic CP[b] (GMFCS level I [*n* = 14]) and 14 age- and sex-matched typically developing controls performed an incremental lateral step-up test across four levels of progressive difficulty (increasing step heights)	• **Lower PFC activity in CP than controls, even after controlling for worse task performance** • PFC activity in CP unrelated to lateral step-up test performance, unlike controls in whom greater PFC activity is related to better lateral step-up test performance at the most challenging task condition

Significant study findings are highlighted in Bold font.

[a]Type of CP not specified; UCP assumed from mention of 'affected side' in fNIRS preprocessing.

[b]Type of CP not specified; UCP (*n* = 12) and BCP (*n* = 2) on request from authors.

Abbreviations: BCP, bilateral cerebral palsy; CIMT, constraint-induced movement therapy; CP, cerebral palsy; fNIRS, functional near-infrared spectroscopy; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; HABIT, Hand–Arm Bimanual Intensive Training; MACS, Manual Ability Classification System; PEDI-CAT, Pediatric Evaluation of Disability Index – Computer Adaptive Test; PFC, prefrontal cortex; RAGT, robot-assisted gait training; sEMG, surface electromyography; SMC, sensorimotor cortex; UCP, unilateral cerebral palsy.

Table 2.S8: Technical specification for fNIRS data collection and processing

First Author (Year)[Ref]	Task Protocol	fNIRS Technical Specifications	Choice of Hemoglobin[Rationale]; fNIRS outcomes	fNIRS Processing
Khan (2010) [44]	Block design (30s pre-task rest → 10 blocks of 15s tapping-25s rest); acquisition time ~450s.	Wired system (CW5, TechEn) with 16 sources (λ_1 = 690nm; λ_2 = 830nm), 16 detectors → 28 long-distance channels (spacing = 3.2cm; 6x20cm^2 field of view), no short-distance channels and auxiliary measures of respiratory belt & pulse oximeter time-synchronized with fNIRS. Sampling = 100Hz (down-sampled to 20Hz). No channel registration or co-registration to subject-specific MRI scan.	**HbO**[1,2,3] 1. Spatial metrics: - Distance from midline - Difference in activation area 2. Temporal metrics: - Duration of activation - Time-to-peak activity 3. Similarity analysis: Pixels with similar temporal patterns as primary activation area	Processing software: HOMER • Signal quality: Visual inspection of fNIRS data → removed data of subjects with thick, dark hair and poor signal quality (Removal criteria and number of channels removed: NR) • Filtering: Butterworth filter with cutoffs 0.01 - 2Hz (Order: NR) • Motion artifact correction: Principal component analysis (Components removed: First 2 eigenvectors) • Systemic physiology correction: Adaptive filtering (least mean squares) using respiratory belt and pulse oximeter signal • Order of correction: Bandpass filter → block averaging for baseline drift correction (normalized using average signal from 5s prior to each task period) → Principal component analysis → Adaptive filtering
Tian (2010)[41]	*Same as Khan et al., 2010*[63]	*Same as Khan et al., 2010 [44],* except data down-sampled to 10Hz	**HbO**[2,3] 1. Spatiotemporal: - Activity volume - Activity geometric center 2. Laterality Index	Processing software: HOMER • Signal quality: Visual inspection of task video recordings + synchronous sEMG for unwanted motion → removed contaminated epochs + subjects with consistent motion artifacts (Removal criteria = ≥60% of dataset contaminated; Number of channels removed: NR) • Filtering: $Butterworth filter with cutoffs 0.01 - 3Hz (Order: NR) • Motion artifact correction: Visual inspection and manual removal of contaminated data • Systemic physiology correction: NR • Order of correction: Bandpass filter → block averaging (average signal over 15s task; normalization time NR)
Hervey (2014)[42]	Block design (180s pre-task rest → 8 blocks of 15s tapping-25s rest); acquisition time ~420s.	Wired system (CW6, TechEn) with 16 source optodes (λ_1 = 690nm; λ_2 = 830nm), 32 detectors → 84 long-distance channels (spacing = 3cm; 11x20cm^2 field of view), 8 short-distance channels (spacing = 1.5cm). Sampling = 25Hz (down-sampled to 20Hz).	**HbO**[NR] Qualitative analyses of fNIRS activation 'maps' comparing activity patterns in 'finger-tapping maps' versus 'mirror maps'	Processing software: HOMER • Signal quality: Visual inspection of fNIRS data → removed contaminated epochs with obvious artifacts (Removal criteria and number of channels removed: NR) • Filtering: $Butterworth filter with cutoffs 0.01 – 0.4Hz (Order: NR) • Motion artifact correction: Visual inspection and manual removal of contaminated data • Systemic physiology correction: Adaptive filtering (least mean squares) using one short-separation channel with least motion artifacts (≤1) as reference signal • Order of correction: Bandpass filter → Adaptive filtering
Cao (2015)[43]	Block design (180s pre-task rest → 8 blocks of 15s tapping-25s rest); acquisition time ~420s.	*Same as Hervey et al., 2014*[42] except no down-sampling.	**HbO**[1,2,3]; 1. Spatiotemporal: - Time-to-peak/duration 2. Laterality Index 3. Resting-state functional connectivity via synchronization likelihood (cutoff ≥ 0.6)	Processing software: HOMER • Signal quality: Visual inspection of fNIRS data → removed contaminated epochs with obvious motion artifacts (Removal criteria and number of channels removed: NR) • Filtering: $Butterworth filter with cutoffs 0.01 – 0.4Hz (Order: NR) • Motion artifact correction: Visual inspection, manual removal of contaminated data • Systemic physiology correction: Adaptive filtering (least mean squares) using one short-separation channel with least motion artifacts (≤1, removed by spline interpolation as reference signal, and principal component analysis • Order of correction: Bandpass filter → Adaptive filtering & principal component analysis

Chaudhary (2014)[352]	Block design (30s pre-rest → 5 blocks of 30s task-30s eyes closed rest)	Custom-developed system with 2 sources (*λ = 785nm), 2 detectors → 2 long-distance channels (spacing: NR), no short-distance channels or auxiliary measures. Sampling = 4.76Hz.	**HbT**[4]; 1. Mean ∂HbT 2. Laterality index	Processing software: NR • Signal quality: NR • Filtering: Bandpass filter with cutoffs 0.0016 – 0.3Hz (Type and order: NR) • Motion & systemic physiology correction: NR • Order of correction: NR
Kurz (2014)[46]	Block design (30s walking - 30s rest, 5 trials per session) for 2 sessions performed sequentially	Wired system (ETG-4000, Hitachi) with 8 sources (λ_1 = 695nm; λ_2 = 830nm), 8 detectors → 24 long-distance channels (spacing = 3cm), no short-distance channels or auxiliary measures. Sampling = 10Hz.	**HbO**[NR]; 1. Mean of maximum ∂HbO per RoI (regional) and across all channels (global)	Processing software: NR • Signal quality: NR • Filtering: High-pass filter with cutoffs 0.01 Hz (Type and order: NR) and • Motion artifact correction: Moving average (window = 5s) • Systemic physiology correction: Principal component analysis (Components removed: < 0.25 correlation with reference waveform → Upward slope at walking oset, 5s time-to-peak, 25s peak duration, 5s downward slope) • Order of correction: Filter → Principal component analysis → Block averaging (normalized using mean of signal from 2.5s prior to onset of walking)
Sukal-Moulton (2018)[48]	Block design (8 blocks of 15s task → 25-35s rest); rest periods between tasks	Wired system (CW6, TechEn) with 8 sources (λ_1 = 690nm; λ_2 = 830nm), 16 detectors → 45 long-distance channels (spacing = 2.24 - 3.65cm), no short-distance channels or auxiliary measures. Sampling = 50Hz.	**HbT**[5,6]; 1. GLM-based beta (β) values for HbT 2. Extent of activity 3. Magnitude of activity 4. Laterality index 5. Max. activity location	Processing software: NIRS Toolbox • Signal quality: NR • Filtering: NR • Motion & systemic physiology correction: Auto-Regressive Iterative weighted robust least squares regression • Order of correction: NR
de Campos (2020)[45]	Block design (30s pre-task rest → 8 blocks of 15s task → 20-30s rest)	Wired system (CW6, TechEn) with 8 sources (λ_1 = 690nm; λ_2 = 830nm), 16 detectors → 42 long-distance channels (spacing = 2.5cm-3.3cm), 2 short-distance channels (spacing = 1cm). Sampling = 50Hz.	**HbT**[5]; 1. GLM-based beta (β) values for HbT 2. Magnitude of activity 3. Laterality index	*Same as Sukal-Moulton et al., 2018*[48]
Sukal-Moulton (2020)[47]	*Same as Sukal-Moulton et al., 2018*[48]	*Same as Sukal-Moulton (2018)*[48] and *de Campos (2020)*[45]; common 8 source, 14 detector set → 42 long-distance channels	**HbT**[5,7]; 1. GLM-based beta (β) values for ∂HbT 2. Extent of activity 3. Magnitude of activity 4. Laterality index	*Same as Sukal-Moulton et al., 2018*[48]
Surkar (2018)[57]	Block design with 3 conditions (30s pre-task rest → 4 blocks of 30s task → 30s rest/condition)	Wired fNIRS system (fNIR Devices LLC) with 2 sources (λ_1 = 730nm; λ_2 = 850nm), 2 detectors → 4 long-distance channels (spacing = Fixed, unspecified distance), no short-distance channels or auxiliary measures. Sampling = 2Hz.	**HbO**[8]; 1. Mean ∂HbO (full task epochs) averaged across hemispheres	Processing software: Manufacturer software (fNIRSoft) • Signal quality: Visual inspection of fNIRS data → Saturated signal and motion artifacts identified (Removal criteria and number of channels removed: NR) • Filtering: Low-pass with cutoff 0.1Hz, High-pass with cutoff 10 Hz (Type = Digital; Order = 4th) • Motion artifact correction: Manual removal of waveforms with visually identified saturated signal and motion artifacts • Systemic physiology correction: NR • Order of correction: Filter → Block averaging (normalized using mean of signal from 10s prior to task onset)

Surkar (2018)[59]	*Same as Surkar et al., 2018[57]*	*Same as Surkar et al., 2018 [57]*	**HbO**[8]; 1. Maximal ∂HbO (full task epoch) averaged across hemispheres	Processing software: Manufacturer software (fNIRSoft) • Signal quality: NR • Filtering: Low-pass with cutoff 0.1Hz (Type = Finite impulse response; Order = 20th) • Motion artifact and systemic physiology correction: NR • Order of correction: Filter → Block averaging (normalized using mean of signal from 25s - 5s prior task onset)
Surkar (2021)[58]	*Same as Surkar et al., 2018[57]*	*Same as Surkar et al., 2018 [57]*	*Same as Surkar et al., 2018[57]*	*Same as Surkar et al., 2018[57]*
Perpetuini (2022)[56]	Block design (10 trials of 30s robot-assisted walking → 30s rest)	Wireless fNIRS system (PHOTON CAP, Cortivision) with 16 source optodes (λ_1 = 760nm; λ_2 = 850nm) and 10 detectors forming 34 long-distance channels (spacing: NR), 4 short-distance channels (spacing: NR). Sampling NR.	**HbO and HbR** 1. GLM-based beta (β) values for ∂HbO and ∂HbR for each RoI	Processing software: NIRS-SPM • Signal quality: NR • Filtering: Band-pass with cutoff 0.01 – 0.4Hz (Type = Butterworth digital; Order = Zero-lag 3rd) • Motion artifact correction: Wavelet-based algorithm • Systemic physiology correction: General linear model (ordinary least squares) regression using short-separation channel • Order of correction: NR
Zhang & Xu (2023)[351]	Single-trial design (10 min eyes-closed rest → 10 min task)	Wireless fNIRS system (Cortivision Nirsmart, Danyang Huichuang Medical Equipment) with 18 sources (λ_1 = 760nm; λ_2 = 850nm), 12 detectors → 34 long-distance channels (spacing = 3cm); No short-distance channels or auxiliary measurement. Sampling = 10Hz.	**HbO**[NR] 1. Hemodynamic response via wavelet amplitude index per RoI 2. Laterality index 3. Functional connectivity via wavelet phase coherence per RoI pair 4. Hemispheric Autonomy Index 5. Effective connectivity via coupling strength & coupling direction	Processing software: MATLAB (Toolbox/software: NR) • Signal quality: Signal-to-Noise ratio of fNIRS data (Removal criteria: ratio < 2; Number of channels removed: NR) • Filtering: Band-pass with cutoff 0.01 – 0.2Hz (Type = NR; Order = 4th) • Motion artifact correction: Temporal derivative distribution repair • Systemic physiology correction: Principal component analysis (Components removed: NR) • Order of correction: Temporal derivative distribution repair → Filtering → Conversion to Hb concentration → Principal component analysis → Wavelet transform (complex Morlet wavelet)
Xie (2024)[353]	Single-trial design (5 min rest → 6 min task)	*Same as Zhang & Xu et al., 2023[351]*	**HbO**[NR] 1. Functional connectivity via Phase-locking values 2. Complex network analysis via clustering coefficients 3. Network efficiency (global, local) 3. Dynamic and effective network analysis	Processing software: MATLAB (Toolbox/software: NICA[435]) • Signal quality: Signal-to-Noise ratio of fNIRS data (Removal criteria: ratio < 2; Number of channels removed: NR) • Filtering: Band-pass with cutoff 0.01 – 0.1Hz (Type = Butterworth; Order = 4th) • Motion artifact correction: Temporal derivative distribution repair • Systemic physiology correction: Common average reference spatial filtering • Order of correction: Conversion to Hb concentration → Temporal derivative distribution repair → Common average reference spatial filtering → Bandpass filtering → Functional connectivity analyses

Licea & Khan (2024)[135]	Single-trial design (20s stepping task → 20s rest) for 4 conditions of incremental difficulty	Wireless fNIRS system (Portalite, Artinis) with 3 sources (λ_1 = 750nm; λ_2 = 850nm), 1 detector → 3 spatially overlapping long-distance channels (spacing = 3, 3.5, 4cm; Only 3cm channel used); No short-distance channels or auxiliary measurement. Sampling = 50Hz.	**HbO and HbR** 1. Mean ∂HbO and ∂HbR (full task epochs) averaged across hemispheres	Processing software: Homer3 • Signal quality: [#]Visual inspection of fNIRS data (motion artifacts) and power spectral density plots (cardiac pulsation at 1-2Hz) (removal criteria and number of channels removed: NR) • Filtering: Band-pass with cutoff 0.01 – 0.09Hz (Type = [$]Butterworth; Order = 4th) • Motion artifact correction: Hybrid spline interpolation-Savitzy-Golay method • Systemic physiology correction: Principal component analysis (Components removed = 80% of spatially covarying signal) Order of correction: Principal component analysis → Hybrid Spline - Savitzky-Golay method → Filtering → Block averaging (normalized using mean of signal from 5s prior to task onset

Abbreviations: GLM, General linear model; HbO, Oxyhemoglobin; HbR, Deoxyhemoglobin; HbT, Total hemoglobin; NR: Not reported; sEMG, Surface electromyography; λ, Wavelength emitted; ∂, Change in hemoglobin concentration; [$]Butterworth filter assumed as default option within HOMER program; *Single-wavelength system with wavelength used close to isobestic point for total hemoglobin; [#]Personal communication.

[Number]Rationale for choice of hemoglobin chromophore: [1]High correlation of HbR with HbO; [2]Lower signal amplitudes of HbR makes it susceptible to cross-talk from HbO; [3]Lower signal amplitudes of HbR makes it susceptible to interference from physiological artifacts. [4]Custom fNIRS device emits single wavelength near isobestic point (HbT absorption highest), precluding separate HbO or HbR assessment; [5]Incorporates both aspects of neurovascular coupling; [6]Robust against pial vein artifacts; [7]robust against artifact arising from blood flow in superior sagittal sinus directly overlying leg area of primary motor cortex; [8]Greater sensitivity of ∂HbO to neural changes than HbR.

Addendum: Summary of fNIRS methodology across studies

Most studies (n=13) used a block design with alternating rest-task periods (duration range: 25-35 s, most commonly 30 s) repeated multiple times (range: 4-10 repetitions). Three studies (135, 351, 353) used a single-trial protocol, with Licea et. al. conducting a trial-rest block at each of the 4 'levels' of a progressive lateral step-up task (135), in contrast to a single pre-trial rest-task epoch used by Zhang et al. for the upper limb (351) and Xie et al. for the lower limb (353). The number of movement repetitions per task varied widely across studies, depending on cues to guide movement frequencies (e.g., 450-900 finger tapping repetitions (41, 44), ≤ 67 m of treadmill walking (46), or 80 simulated pours versus 120 hand-squeezes (45)). Most studies reported changes in concentration of oxyhemoglobin (n = 9) or total hemoglobin [65-68]. Two studies reported concentration changes in both oxy- and deoxyhemoglobin (56, 135), in accordance with best practices (402). All studies used commercially available continuous-wave fNIRS devices, except for one pilot study (352) that used a custom-developed fNIRS system. More recent studies used wireless, portable devices (56-59, 135, 351, 353), while early studies (41-44, 46, 352) and 3 NIH-based studies used wired fNIRS systems with limited portability (45, 47, 48). Physical characteristics impacting fNIRS data quality (e.g., skin type, hair color) were reported only in two studies (47, 48). Sampling frequency for fNIRS data were reported for all studies except one (56), with values varying across studies (range = 2-100 Hz), with 50 Hz being the most frequently used (45, 47, 48, 135). All studies used the International 10-20 EEG system for NIRS optode placement, but optode registration for cortical localization was performed in only two studies using motion capture (48) or 3-dimensional digitization (56). Template design ranged from 2-4 channel setups for imaging the PFC (57-59, 135, 352) to a wide 84-channel setup extending over the primary sensorimotor, pre- and supplementary motor cortices (42, 43). Most studies imaged the SMC in isolation (41-48), or in conjunction with the prefrontal cortices (56, 351, 353). Five studies imaged the prefrontal cortices in isolation (57-59, 135, 352). The software most commonly used for fNIRS data pre-processing was the original HomER (436) software ((41-44)), followed by the NIRS Toolbox (437, 438) used in 3 studies (45, 47, 48) or manufacturer software (57-59). Signal quality assessment was performed in half the studies using either visual inspection alone (41-44, 57, 135) or in combination with video and EMG data recordings (41). Two studies by the same group (351, 353) used an objective quantitative assessment of signal-to-noise ratio (SNR < 2) to identify and remove low-quality channels. No study reported the number of channels discarded, or the number of subjects excluded following signal quality evaluation.

Data filtering was performed in all studies except a triad of studies conducted at the NIH (45, 47, 48) that all used an auto-regressive iterative weighted least squares robust linear regression (AR-IRLS) algorithm that does not require data filtering (439). Most studies reported band-pass filtering (n=10), most commonly with a high-pass cut-off frequency of 0.01 Hz (range = 0.0016-10 Hz) and low-pass cut-off frequencies of 0.1 Hz or 0.4Hz (range = 0.09-2 Hz) or a moving average filter (46). One study reported only using a low-pass filter (0.1 Hz cut-off) (59). Methods for correcting motion artifacts were reported in a majority of studies (n = 10), with visual inspection and removal of contaminated epochs or waveforms being the commonest reported method (n=7), followed by the temporal derivative distribution repair (TDDR, (440)) method (351, 353). Individual studies also reported using principal component analyses (PCA) alone (46) or in combination with a spline interpolation-Savitzky Golay smoothing filter (441) as a hybrid method (135) or a wavelet-based filter (56). Three studies used the AR-IRLS algorithm (439) that accounts for motion artifacts, while one study did not report specific methods for motion artifact correction (352). Auxiliary measurements to account for contamination from systemic physiology were recorded in 6 studies, with two studies collecting concurrent pulse oximetry and respiratory data (41, 44) and 4 studies using short-separation channels (number of channels: 2-8; range of distances: 1-1.5 cm) (42, 43, 45, 56) to capture blood flow changes in superficial, non-neuronal tissues. Other processing methods to remove non-neuronal signal components included PCA (46, 135, 351) and/or adaptive filtering using concurrently captured cardiorespiratory data (44), short-separation channel data regression (42, 43, 56), the AR-IRLS algorithm (45, 47, 48) or common average reference-based spatial filter (442) used in 1 study (353). Notably, no correction of systemic physiological contamination was undertaken in 5 studies (41, 45, 47, 48, 352). Cortical activity was quantified via block averaging (46, 57-59, 135, 352), with the general linear model using ordinary least squares (41-44, 56) or via the AR-IRLS algorithm (45, 47, 48)), with the exception of one study that used a complex Morlet wavelet transform (351).

Critical Appraisal of fNIRS Methods

Methodological practices varied widely across studies included in this review. Most recent fNIRS studies in CP used wireless and portable fNIRS systems, mirroring a general trend in the fNIRS community to transition away from wired systems (443). Only one study used an objective quantitative metric for channel-wise assessment of fNIRS signal quality, with a majority reporting visual inspection methods that are highly subjective, and dependent on assessor expertise/experience. Recent technical advances have seen the emergence of (semi)-automated, quantitative measures of signal quality (396, 397) that should be incorporated in future fNIRS research in CP. An issue reported in some of the included studies (42, 135) was the high number of movement artifacts present in the data, which may be best avoided by optimally designed experimental protocols (379), or when present, managed through signal processing algorithms (439, 441, 444). A major concern in most fNIRS studies is the high potential for signal contamination from changes in systemic physiology (e.g., heart rate, respiratory rate, blood pressure) due to the passage of light through superficial (non-cortical) tissues that also experience blood-flow changes (211). The gold-standard for managing this ubiquitous contamination is the use of short-separation channels (ideally <1 - 1.5cm distance (445)), which was used to regress out superficial blood flow data only in some studies with CP (42, 43, 56). While alternate means to account for superficial signal contamination have been proposed (399) and were used in some included studies (principal component analysis (46, 135, 351), adaptive filtering (44) and AR-IRLS algorithm (45, 47, 48)), five studies did not report any correction for systemic physiology (41, 45, 47, 48, 352), and conclusions drawn from these studies must be interpreted with caution. Similarly, only two studies followed recently published best practice recommendations [79] on reporting changes in both hemoglobin chomophores (HbO, HbR) [59, 73], which mirrors concerns raised within the fNIRS community on inconsistent reporting practices (446). Further, Perpetuini et al. reported

unidirectional changes in HbO and HbR concentrations (e.g., both increased in the PFC), with conclusions based only on HbO changes (56). In normal physiological states, neural activity provokes neurovascular coupling, with HbO and HbR signals showing anti-correlated pattern (increase in HbO that is ~three-fold greater than the decrease in HbR), with positive correlation observed with motion artifacts (447) and systemic physiology contamination (448). Though violations to this anti-correlation assumption have been reported in the immature or compromised nervous system (e.g., in infancy (449), ischaemia (450); see (451) for detailed review), caution must be exercised in the interpretation of results of studies showing positive HbO-HbR correlation patterns, till scientific consensus is reached on the complex role and impact of altered neurovascular coupling in neurodevelopmental disorders (452).

CHAPTER 3

DIFFERENTIAL EFFECTS OF TIMING CONSTRAINTS AND TARGET MOTION ON PLANNING AND EXECUTION OF GOAL-DIRECTED REACHING IN CHILDREN WITH CEREBRAL PALSY

[1] Khan, O.A., Barany, D., Singh, T., Rahman, S., Modlesky, C.M. 2025. *To be submitted to a peer-reviewed journal*.

Abstract

Introduction: Children with cerebral palsy (CP) exhibit impaired motor planning and execution deficits when reaching for stationary objects, but the influence of time constraints and target motion on movement outcomes has not been systematically investigated. This study aimed to determine if children with CP exhibit similar deficits in motor performance and planning when reaching for stationary and moving targets compared to typically developing control children, and to relate robotic metrics to standardized clinical assessments.

Method: Twenty-nine children with spastic CP (5-11y; Manual Ability Classification System level I-II) and 29 age- and sex-matched typically developing control children completed two robotic tasks assessing unimanual reaching to either stationary or moving targets. Both arms were tested, with task difficulty modulated by varying time allowed to hit the target (500, 625, 750, and 900 ms time constraints; 10 trials/block). Group differences in motor performance (accuracy, spatial error, peak velocity, path variability) and planning (reaction time, initial movement angle) were analyzed using linear mixed-effects models. Relationships between robotic metrics and clinical assessment scores were evaluated using age-controlled partial Spearman correlation.

Results: Children with CP exhibited worse motor performance (i.e., lower accuracy, greater spatial errors, slower peak velocities, and higher path variability) than controls across both tasks, with deficits most pronounced with the non-preferred arm and exaggerated with increasing time pressure. Children with CP also displayed impaired motor planning (i.e., slower reaction time and lower initial angles than controls) across both tasks, though deficits were more consistent across time constraints. Better performance metrics during non-preferred arm reaching were related to higher clinical scores in CP (r range = 0.552–0.635, all $p < 0.05$). Better planning metrics across tasks were linked to better clinical performance in those with CP (r range = -0.555–0.608, all $p < 0.05$).

Conclusion: Children with CP exhibit arm- and task-specific impairments in motor planning and performance that are differently influenced by time constraints, and separately linked to clinical performance. Robotic assessments successfully captured these subtle yet clinically meaningful deficits, supporting their potential for delineating individual motor profiles and identifying therapeutic targets for tailored rehabilitation following early brain injury in CP.

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3.1. Introduction

Goal-directed reaching is an integral component of daily activities such as catching a ball or grabbing an object that is embedded in real-world interactions and play in young children. For children with cerebral palsy (CP), these simple motor tasks reveal subtle and pernicious challenges in movement planning, coordination, and execution (453, 454). As a lifelong condition of impaired posture and movement occurring due to brain injury or malformation early in development (455), CP is commonly recognized as the most common cause of childhood-onset motor disability (456). Upper limb dysfunction is observed in more than 60% of children with CP (5), and is especially disabling in childhood, where it limits participation in self-care, play, academic, and recreational pursuits (7, 113). While a growing body of research has described kinematic deficits during simple reaching behaviors in CP (457), most studies have focused on interactions with stationary objects in unconstrained settings that do not adequately reflect the complex cognitive-motor processing underlying manual abilities in this group (121, 458).

Despite growing recognition that motor planning impairments are highly prevalent (8) and persistent across development in CP (34), their specific contribution to motor performance during daily motor tasks remains insufficiently understood (35, 36). Motor tasks such as catching or striking a ball appear simple, but require complex neural computations for rapid adjustments to target movement, judicious attentional shifts to environmental cues, and seamless adaptation to changing task contexts and timing constraint (30). These demands engage multiple higher-order cortical processes to enable sensorimotor integration, visuospatial prediction, and attentional regulation to achieve task goals (248, 459). While the coordinated recruitment of these neural networks is entrained through voluminous motor practice, and freedom of exploration and object interaction in typically developing infants (460), early disruptions in brain network development in CP renders this integration inefficient at best, and ineffectual at worst. However, conventional kinematic-based assessments of reaching are unidimensional (461), translate poorly to real-world

function (462), and are limited in their ability to probe both planning and performance abilities across varying task contexts. Interception tasks involving moving targets offer an ecologically valid framework to probe these dynamic processes. Through controlled manipulation of time restrictions and high-resolution kinematic measurement, these tasks can provide critical insights into how children with CP prepare for, execute, and adapt their movements under time pressure, shedding light on these complex yet understudied aspects of behavior.

Few studies have systematically examined how children with CP respond to interception demands across varying temporal constraints (30), or whether such task-induced challenges differentially affect motor planning and execution across limbs. This gap is particularly important given the high prevalence of bilateral yet asymmetrical motor impairments in CP (463), where differences between the preferred and non-preferred arm may reflect distinct neural strategies or compensatory mechanisms (464). Additionally, it remains unclear whether motor planning abilities under time pressure relate meaningfully to functional outcomes captured by standardized clinical assessments of manual ability. We (464) previously explored the importance of task context in modulating cognitive-motor engagement in children with CP using a stationary reaching paradigm under varying time constraint. Reduced prefrontal cortex activity under high time pressure was linked to lower reaching accuracy in the non-preferred arm, suggesting insufficient recruitment of action planning neural systems during this task in CP. In contrast, interception tasks provide continuous visual cues and external timing, which may help scaffold motor planning by engaging more automatic visuomotor pathways. This enhanced engagement and attentional focus may support more effectively planning and execute of goal-directed interception compared to stationary target reaching, but empirical evidence comparing motor performance and planning across these tasks is lacking. Robotic technologies offer a powerful platform to address these gaps (465) by enabling the simultaneous capture of discrete metrics of motor planning (e.g., reaction time, initial trajectory) and performance (e.g., accuracy, spatial error, velocity) with high reliability and precision (12, 466). When combined with interception-based assessment protocols, these tools can

help dissect how children with CP generate and adjust motor plans in response to environmental constraints (244) —offering not only mechanistic insight, but also the potential to identify sensitive behavioral markers of impairment that may inform individualized therapeutic approaches.

This study leveraged a robotic interception paradigm to systematically evaluate motor planning and performance in children with CP across time constraints during stationary target reaching and moving target interception tasks. By combining graded temporal restrictions with bilateral arm testing for both tasks, we aimed to determine the effects of time constraints on movement performance and planning across the two tasks in children with CP. We expected children with CP to exhibit impaired motor performance, evidenced by lower accuracy, higher spatial errors, and slower peak velocities than typically developing peers, with deficits more pronounced during stationary target reaching and under high time constraints. We further hypothesized impaired motor planning in CP, reflected by longer reaction times, lower initial movement angles, and greater path variability than controls, with deficits similar across both tasks, and all time constraints. Additionally, we aimed to determine relationships between robotic measures and clinical assessments of fine and gross manual ability, and predicted better robotic metrics would be related to higher clinical scores in children with CP. This approach aims to disentangle arm-specific contributions of planning versus execution deficits across task contexts (i.e., target motion and time constraints), providing a holistic assessment framework for identifying individualized therapeutic targets and advancing the understanding of how children with CP adapt, or fail to adapt, to real-world movement challenges.

3.2. Methods

Recruitment

We recruited children with spastic CP (age 5-11 y) alongside typically developing control children matched to the CP group by age (± 1.5 y), sex, and race for a larger controlled trial (NCT03484078). Recruitment occurred via outreach to schools, clinics, the Cerebral Palsy

Foundation, and Children's Healthcare of Atlanta between March 2019 and March 2024. Controls were required to have no neurological diagnoses, height and body mass between 5-95th percentiles on age- and sex-based norms, and no participation in high-level sports. Exclusion criteria included (1) inability to follow simple verbal instructions, (2) severe limitations in handling objects and performing simple manual tasks (Manual Ability Classification System (MACS) level V), [3] botulinum toxin injections within six months of study enrollment, or [4] significant visual or musculoskeletal impairments that would prevent robotic assessments. The Institutional Review Board at the University of Georgia approved the study, and parental informed consent and participant assent were obtained at study enrollment.

Physical characteristics and clinical assessments

Height was measured with a stadiometer (Seca 217; Seca GmbH & Co., Germany) and body mass was assessed with a digital scale (Detecto 6550, Cardinal Scale, USA). Percentiles for height, body mass, and body mass index (BMI) were computed using normative data for the United States population (467). Hand preference was assessed with the Edinburgh Handedness Inventory-Short Form (468). Manual ability and gross motor function was classified using the MACS (221) and the Gross Motor Function Classification System (GMFCS) (469), respectively. Muscle tone was assessed using the Hypertonia Assessment Tool (HAT) (470).

Manual ability was assessed using the Box and Blocks Test (BBT) (228) and the Purdue Pegboard Test (PPT) (116). The BBT measures unimanual capacity as the number of 1-inch blocks moved across a partitioned box within 60 seconds (225), with a higher number of blocks transferred indicating better gross manual ability. The PPT measures unimanual dexterity as the number of pegs sequentially placed into a standardized pegboard within 30 seconds (229), with a higher number of pegs secured indicating better fine manual ability (230).

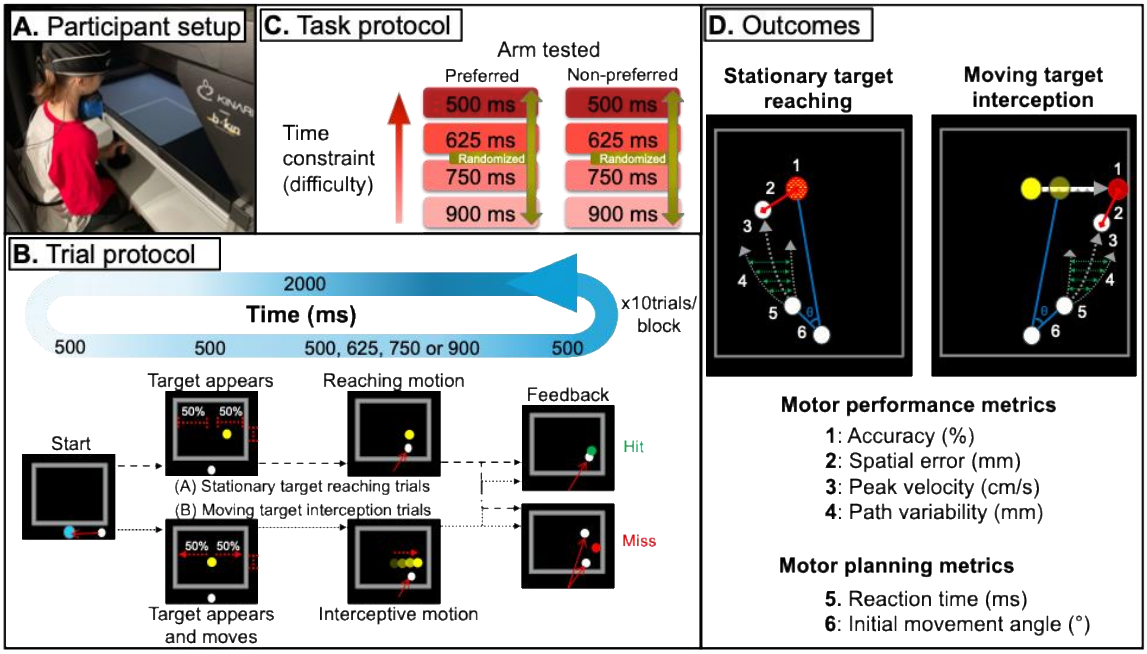

Figure 3.1. Study methods. (**A**) Participant setup depicting seated position and unimanual grasp of the robotic manipulandum (KINARM). (**B**) Trial protocol and (**C**) task protocol for the stationary target reaching and moving target interception tasks. (**D**) Behavioral outcomes were categorized into motor performance and motor planning metrics.

Experimental setup

The experimental setup (**Fig. 3.1A**) has been detailed in previous work (266, 464). Participants were seated and viewed task stimuli projected onto a semi-transparent mirror. They controlled an on-screen cursor (1 cm white circle) by moving a robotic manipulandum (KINARM End-Point, Ontario, Canada) in the horizontal plane, while the screen occluded visual feedback of their arm. All tasks was performed within a defined workspace (a 34 x 34 cm grey square; **Fig. 3.1B**), where each trial began once the participant held the cursor inside a designated start area (2 cm blue circle) for 500 milliseconds.

Stationary target reaching trials began with a target (1 cm yellow circle) appearing on either side of the workplace (50% probability). Target location was randomized within a constrained spatial range (x-position: ± 1 to ± 6.5 cm lateral to midline; y-position = ± 1.5 cm from workspace center). For each trial, participants were instructed to hit the target as quickly and accurately as possible using the on-screen cursor. Stopping at the target location was not required, with a “hit”

defined as the initial moment the cursor overlapped with the target. Time constraints were imposed by varying the time permitted to hit the target across blocks (500, 625, 750 or 900 ms blocks). Targets turned green when successfully contacted within the allotted time window ("hit"), or turned red if missed or hit after the time constraint had elapsed ("miss").

Moving target interception trials began with the target appearing in the midline (x = 0; y = ±0.5 cm from workspace center) and moved laterally to the left or right with equal probability at a constant velocity. Participants were instructed to intercept the target swiftly and accurately without pausing at its location. Time constraints were applied by modulating target velocity across blocks to alter the time allowed to intercept the target (500, 625, 750, or 900 ms blocks). A successful interception was defined by cursor-target overlap within the time window that turned the target green ("hit"), while failure to intercept resulted in the target turning red upon contact with the workspace boundary. Performance feedback was displayed for 500 milliseconds for each trial, followed by a fixed inter-trial interval of 2000 milliseconds.

Each participant completed four randomized blocks of 10 trials each per arm (**Fig. 3.1C**) for each task, with each participant completing 160 trials overall. Stationary target reaching was always performed first, and the preferred arm was tested first in each task. To minimize learning effects, and ensure task comprehension, a practice block (750 ms time constraint) was allowed prior to testing for each task. Breaks were provided between blocks, arms, and tasks as required, with standardized verbal feedback and encouragement provided at pseudorandom intervals within each block to ensure compliance and optimal engagement.

Data processing

Robotic data were sampled at 1000 Hz with the KINARM and exported into MATLAB (MathWorks, Natick, MA) before undergoing further analysis in Python (v3.10). Hand kinematics, including position and velocity, were smoothened with a low-pass filter (4^{th} order Butterworth, cut-

off = 5 Hz) to reduce high-frequency noise. Task outcomes (**Fig. 3.1D**) were categorized as performance and planning-related metrics.

i. Motor performance outcomes

Task accuracy was defined as the percentage of successful "hits" per block. Spatial error was measured as the Euclidean distance between the target and cursor at the point of movement offset. Since participants were not required to decelerate or stop at the target, movement offset was operationalized as either the moment of initial cursor-target overlap, or the time at which the cursor passed the target's y-coordinate. Peak velocity was identified as the maximum tangential velocity during the trial.

Path variability was computed as the summed standard deviation of mean-normalized trajectory deviations per block, in line with previous work in children with CP (289). Specifically, trials within each block were time-normalized to 150 time points and grouped by target location (for stationary target reaching) or movement direction (for moving target interception) into left- or right-workspace trials. A mean trajectory was computed for each arm as the average trajectory in each half of workspace, for each participant. All trajectories were subsequently normalized by the respective mean trajectory of each workspace division. Lateral standard deviations calculated for each time point of the resultant time- and mean-normalized trajectories were summated to provide an overall measure of reaching movement consistency that also accounts for each participant's individual movement strategy (289).

ii. Motor planning outcomes

Movement onset was determined by identifying when hand velocity surpassed 5% of its first local peak following target appearance. Reaction time was calculated as the latency between target onset and movement onset. Trials were discarded if movement onset could not be determined or if reaction times were implausible (i.e., under 100 ms or exceeding the trial duration). Initial movement angle was calculated 50 milliseconds after movement onset as the angle between the

vector from start position to cursor, and the vector from start position to target. Positive values reflected anticipatory or curve-around trajectories directed ahead of the target, whereas negative values indicated lagging or curve-forward trajectories directed behind or at the target.

Statistical analysis

Statistical analyses were conducted in SPSS (v27.0.1, IBM Corp., Armonk, NY) and RStudio (v2022.07.2). Normality of data was evaluated using skewness, kurtosis, and the Shapiro-Wilk test. Independent t-tests or non-parametric Mann-Whitney *U* tests were used to evaluate group differences in physical characteristics, based on normality. One-sample t-tests were used to assess deviations of physical characteristic percentiles from age- and sex-based 50th percentiles. Separate linear mixed-effect models in RStudio (*lmerTest* package (471)) were used to analyze motor performance (accuracy, spatial error, peak velocity, path variability) and planning outcomes (reaction time, initial movement angle) for stationary target reaching and moving target interception. Models included a combination of fixed effects of group (CP vs. controls), arm (preferred vs. non-preferred), and time constraint (500, 625, 750, 900 ms), with participant included as a random effect across models to account for within-subject correlations from repeated measures. Significant effects were followed by pairwise comparisons (alpha = 0.05) in RStudio (*emmeans* package (472)). Age-controlled partial Spearman rho correlation (*r*) was used to assess relationships between robotic metrics and clinical assessment scores. Effects sizes (Cohen's d (*d*)) were categorized as small (0.2), medium (0.5), or large (0.8) (473).

3.3. Results

Participant characteristics

Twenty-nine children with spastic CP and 29 age- and sex-matched typically developing control children participated in the study (**Table 3.1)**. No different in height, body, or BMI were

observed between groups (all $p > 0.05$), and percentiles did not differ from age- and sex-based 50th percentiles in either group (all $p > 0.05$).

Table 3.1. Physical characteristics of children with cerebral palsy (CP) and typically developing control children (Con).

	CP (n = 29)	Con (n = 29)	*d*	*p*
Age (y)	8.7 ± 2.0	8.5 ± 2.3	0.086	0.744
Sex (male/female)	15/14	15/14	—	—
Race (White/Black/Asian)	24/5/0	25/3/1	—	—
Height (m)	1.31 ± 0.14	1.33 ± 0.15	0.132	0.619
Height %	48 ± 34	64 ± 23	0.540	0.083
Body mass (kg)	29.5 ± 8.5	30.5 ± 10.8	0.108	0.957
Body mass %	50 ± 31	58 ± 25	0.304	0.252
BMI	17.0 ± 2.8	16.8 ± 2.7	0.056	0.932
BMI %	51 ± 32	54 ± 28	0.101	0.738
Arm dominance (right/left)	17/12	28/1	—	—
CP diagnosis (unilateral/bilateral)	17/12	—	—	—
MACS level (I/II)	4/25	—	—	—
GMFCS level (I/II)	23/6	—	—	—
HAT preferred arm	21^{a}/4^{b}/2^{c}/2^{d}	29^{a}/0^{b}/0^{c}/0^{d}	—	—
HAT non-preferred arm	16^{a}/8^{b}/1^{c}/4^{d}	29^{a}/0^{b}/0^{c}/0^{d}	—	—

All values are mean ± SD. % represents percentiles for height, body mass, and BMI. Percentiles did not differ from age- and sex-based 50th percentiles. ^{a}Normal tone, ^{b}spasticity, ^{c}dystonia, ^{d}mixed tone (spasticity with dystonia).

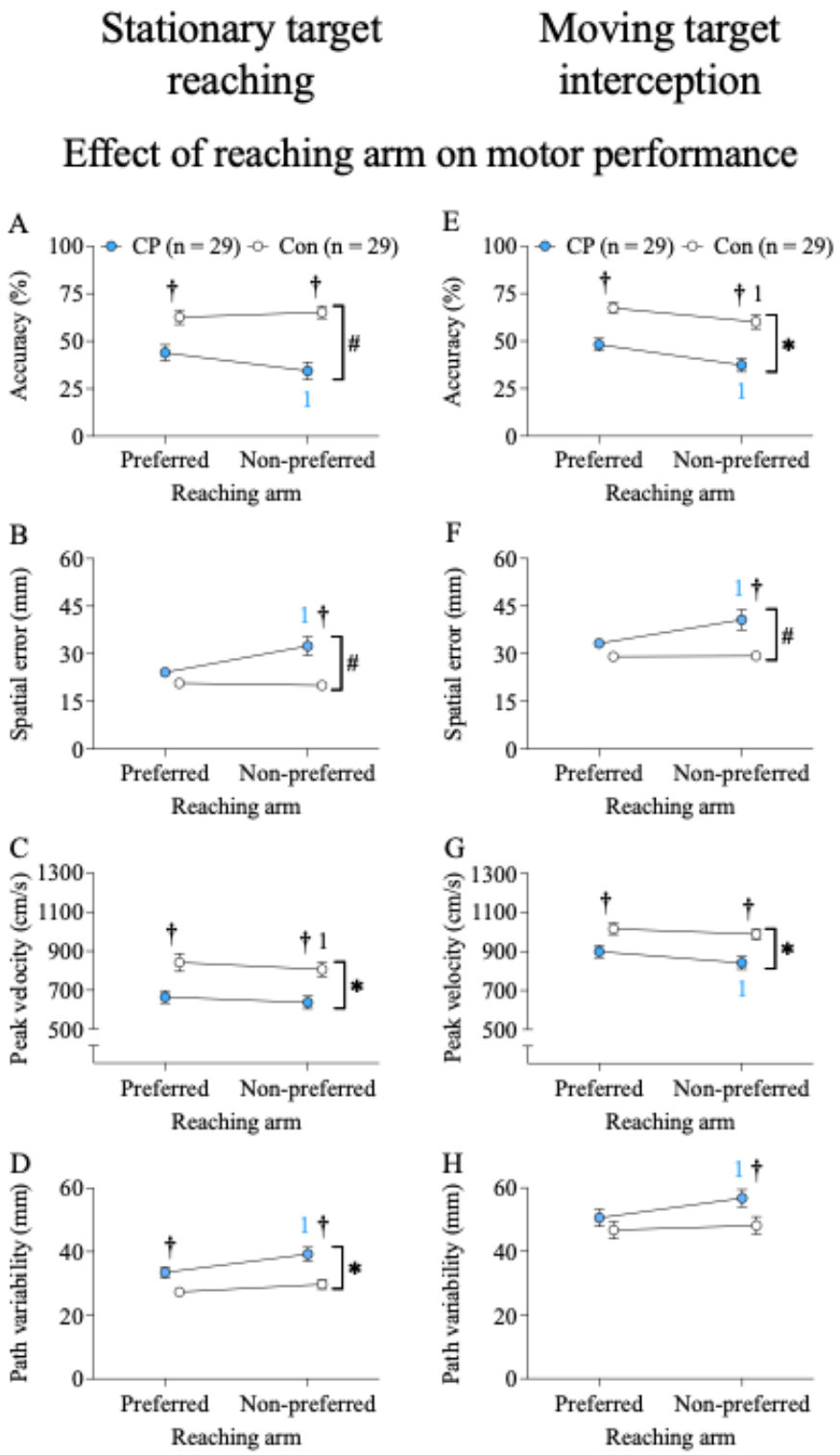

Figure 3.2: Motor performance metrics (accuracy, spatial error, peak velocity, path variability) across reaching arm for stationary target reaching (A-D) and moving target interception (E-H) in children with cerebral palsy (CP) and typically developing control children (Con). All values are mean ± SE. # Group-by-arm interaction, ✱ group effect, † group difference, [1]arm difference (CP, Con).

Motor performance across reaching arm

a. Stationary-target reaching

A group-by-arm interaction for accuracy ($p = 0.013$; **Fig. 3.2A**) indicated children with CP displayed lower accuracy than controls in each arm ($d_{Non\text{-}preferred} = 0.976$, $d_{Preferred} = 0.590$; both $p < 0.05$), and lower accuracy in the non-preferred compared to their preferred arm ($d = 0.302$, $p = 0.006$). A group-by-arm interaction for spatial error ($p < 0.001$; **Fig. 3.2B**) revealed children with CP demonstrated higher spatial error with the non-preferred arm compared to controls ($d = 1.052$, $p < 0.001$) and to their preferred arm ($d = 0.658$, $p < 0.001$). A group effect for peak velocity ($p = 0.001$; **Fig. 3.2C**) indicated children with CP exhibited lower overall peak velocity than controls across arms ($d = 0.772$, $p = 0.001$). Peak velocity was significantly lower with the non-preferred than preferred arm in controls (i.e., $d = 0.160$, $p = 0.039$), but not in those with CP ($d = 0.136$, $p = 0.079$). A group effect for path variability ($p < 0.001$; **Fig. 3.3D**) suggested children with CP displayed higher path variability than controls across arms ($d = 0.626$, $p < 0.001$) and in each arm ($d_{Non\text{-}preferred} = 0.763$, $d_{Preferred} = 0.492$; both $p < 0.05$). Path variability was significantly higher with the non-preferred than preferred arm in children with CP (i.e., $d = 0.461$, $p < 0.001$), but not in controls ($d = 0.191$, $p = 0.092$).

b. Moving-target interception

A group effect for accuracy ($p < 0.001$; **Fig. 3.2E**) revealed lower overall accuracy in children with CP than controls across arms ($d = 0.710$, $p < 0.001$) and in each arm ($d_{Non\text{-}preferred} = 0.772$, $d_{Preferred} = 0.651$; both $p < 0.001$). Accuracy was lower with the non-preferred than preferred arm in controls and children with CP ($d = 0.245$ and 0.364, respectively; both $p < 0.05$). A group-by-arm interaction for spatial error ($p = 0.003$; **Fig. 3.2F**) indicated children with CP demonstrated higher spatial error with the non-preferred arm compared to controls ($d = 0.778$, $p < 0.001$), and to their preferred arm ($d = 0.486$, $p < 0.001$). A group effect for peak velocity ($p = 0.002$; **Fig. 3.2G**)

reflected children with CP exhibited lower overall peak velocity than controls across arms (d = 0.621, p = 0.002). Peak velocity was lower with the non-preferred than preferred arm in children with CP (d = 0.285, p = 0.004), but not in controls (d = 0.138, p = 0.156). While no group effect or group-by-arm interaction was observed for path variability (both $p > 0.05$; **Fig. 3.3H**), children with CP exhibited higher path variability with the non-preferred arm compared to controls (d = 0.395, p = 0.023), and to their preferred arm (d = 0.285, p = 0.014).

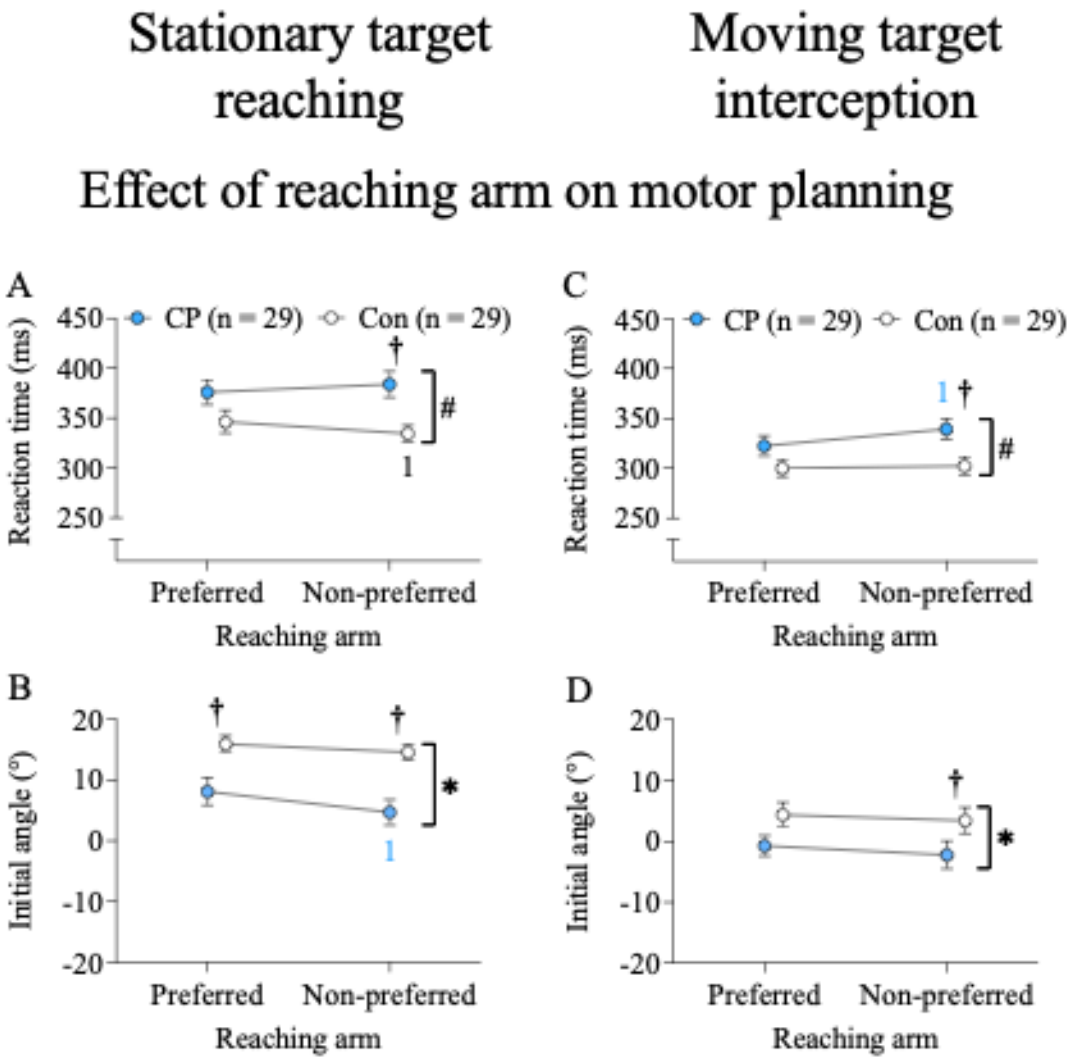

Figure 3.3: Motor planning metrics (reaction time, initial movement angle) across reaching arm for stationary target reaching (A, B) and moving target interception (C, D) in children with cerebral palsy (CP) and typically developing control children (Con). All values are mean ± SE. # Group-by-arm interaction, ✱ group effect, † group difference, [1]arm difference (CP, Con).

Motor planning across reaching arm

a. Stationary-target reaching

A group-by-arm interaction for reaction time ($p = 0.004$; **Fig. 3.3A**) indicated children with CP displayed significantly longer reaction time than controls in the non-preferred arm ($d = 0.711$, $p = 0.003$) but not the preferred arm ($d = 0.424$, $p = 0.073$). Reaction time with the non-preferred compared to the preferred arm was significantly faster in controls ($d = 0.170$, $p = 0.017$), but trended slower in children with CP ($d = 0.118$, $p = 0.096$). A group effect for initial movement angle ($p < 0.001$; **Fig. 3.3B**) indicated children with CP displayed lower overall initial movement angle than controls across arms ($d = 0.607$, $p < 0.001$) and in each arm ($d_{Non\text{-}preferred} = 0.683$, $d_{Preferred} = 0.532$; both $p < 0.05$). Initial movement angle was also lower with the non-preferred than preferred arm in children with CP (i.e., $d = 0.233$, $p = 0.041$), but not in controls ($d = 0.082$, $p = 0.468$).

b. Moving-target interception

A group-by-arm interaction for reaction time ($p = 0.003$; **Fig. 3.3C**) revealed significantly longer reaction time in the non-preferred arm of children with CP compared to controls ($d = 0.657$, $p = 0.008$) and to their preferred arm ($d = 0.300$, $p < 0.001$). A group effect for initial movement angle ($p = 0.031$; **Fig. 3.3D**) suggested lower initial movement angle in children with CP than controls across arms ($d = 0.353$, $p = 0.031$), with significant differences in the non-preferred ($d = 0.365$, $p = 0.044$), but not the preferred arm ($d = 0.341$, $p = 0.059$).

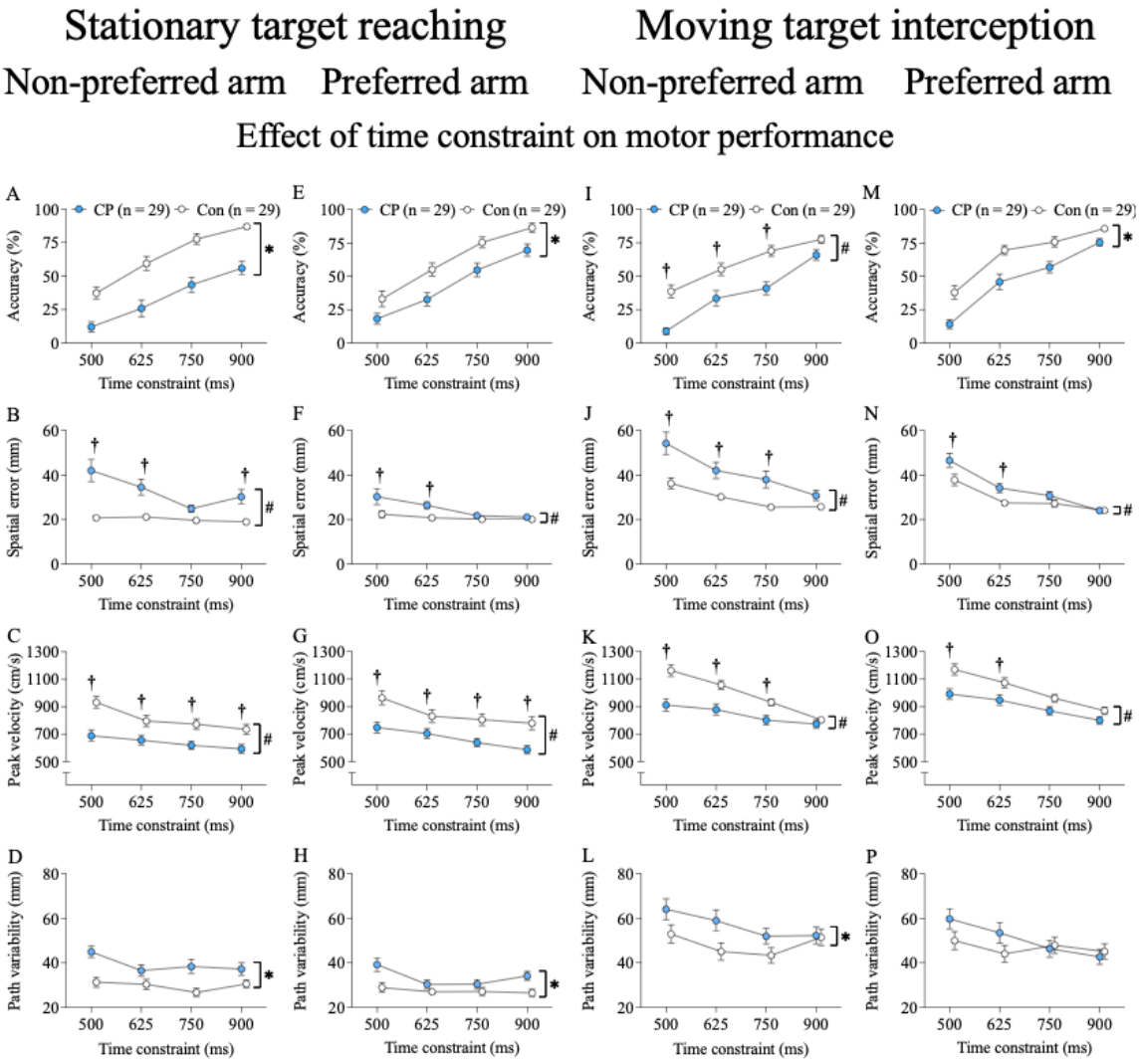

Figure 3.4: Motor performance metrics (accuracy, spatial error, peak velocity, path variability) across time constraints for stationary target reaching (A-H) and moving target interception (I-P) with each arm in children with cerebral palsy (CP) and typically developing control children (Con). All values are mean ± SE. # Group-by-time constraint interaction, ✱ group effect, † group difference.

Motor performance across time constraints

a. Stationary-target reaching

Group effects for accuracy observed in the non-preferred (p < 0.001; **Fig. 3.4A**) and preferred arm (p = 0.002; **Fig. 3.4E**) indicated children with CP displayed lower accuracy than controls across time constraints in each arm ($d_{Non\text{-}preferred}$ *range* = 0.988–1.340, $d_{Preferred}$ *range* = 0.584–0.882; all p < 0.05). Group-by-time constraint interactions for spatial error were observed in

the non-preferred ($p < 0.001$; **Fig. 3.4B**) and preferred arm ($p = 0.041$; **Fig. 3.4F**), with children with CP demonstrating higher spatial error than controls at the more challenging 500 ms and 625 ms time constraints in each arm ($d_{Non\text{-}preferred} = 1.533$ and 0.960, respectively; $d_{Preferred} = 0.883$ and 0.627, respectively; all $p < 0.05$). Similarly, group-by-time constraint interactions for peak velocity were noted in the non-preferred ($p = 0.018$; **Fig. 3.4C**) and preferred arm ($p = 0.045$; **Fig. 3.4G**). Children with CP exhibited lower peak velocity than controls across time constraints in each arm ($d_{Non\text{-}preferred}$ range = 0.683–1.182, $d_{Preferred}$ range = 0.563–0.955; all $p < 0.05$), with group differences most pronounced at the most challenging 500 ms time constraint in both arms. Group effects for path variability in the non-preferred ($p = 0.001$; **Fig. 3.5D**) and preferred arm ($p = 0.005$; **Fig. 3.5H**) indicated greater path variability in children with CP than controls, with the magnitude of differences greatest at the 500 ms time constraint in each arm ($d_{Non\text{-}preferred} = 1.019$, $d_{Preferred} = 0.921$; both $p \leq 0.001$).

b. Moving-target interception

A group-by-time constraint interaction for accuracy in the non-preferred arm ($p = 0.011$; **Fig. 3.4I**) indicated lower accuracy in children with CP than controls at all time constraints (d range = 0.921–1.257, all $p \leq 0.001$) except the slowest 900 ms block ($d = 0.497$, $p = 0.061$). Conversely, a group effect for accuracy was noted in the preferred arm ($p < 0.001$; **Fig. 3.4M**), with children with CP displaying significantly lower accuracy than controls across time constraints (d range = 0.863-1.082, all $p < 0.05$) except the 900 ms block ($d = 0.471$, $p = 0.075$). Group-by-time constraint interactions for spatial error were noted in the non-preferred ($p < 0.007$; **Fig. 3.4J**) and preferred arm ($p = 0.020$; **Fig. 3.4N**), with higher spatial error observed in children with CP than controls at the more challenging 500 ms and 625 ms time constraints in each arm ($d_{Non\text{-}preferred} = 1.117$ and 0.734, respectively; $d_{Preferred} = 0.818$ and 0.624, respectively; all $p < 0.05$). Similarly, group-by-time constraint interactions for peak velocity were noted in the non-preferred ($p < 0.001$; **Fig. 3.4K**) and preferred arm ($p = 0.031$; **Fig. 3.4O**), with lower peak velocity recorded in children with CP than

controls at the 500 ms and 625 ms time constraints in each arm ($d_{Non\text{-}preferred}$ = 1.306 and 0.931, respectively; $d_{Preferred}$ = 0.965 and 0.679, respectively; all $p < 0.05$). A group effect for path variability in the non-preferred arm ($p = 0.030$; **Fig. 3.5L**) indicated overall higher path variability in children with CP than controls, though significant differences were only observed at the 625 ms time constraint ($d = 0.643$, $p = 0.015$).

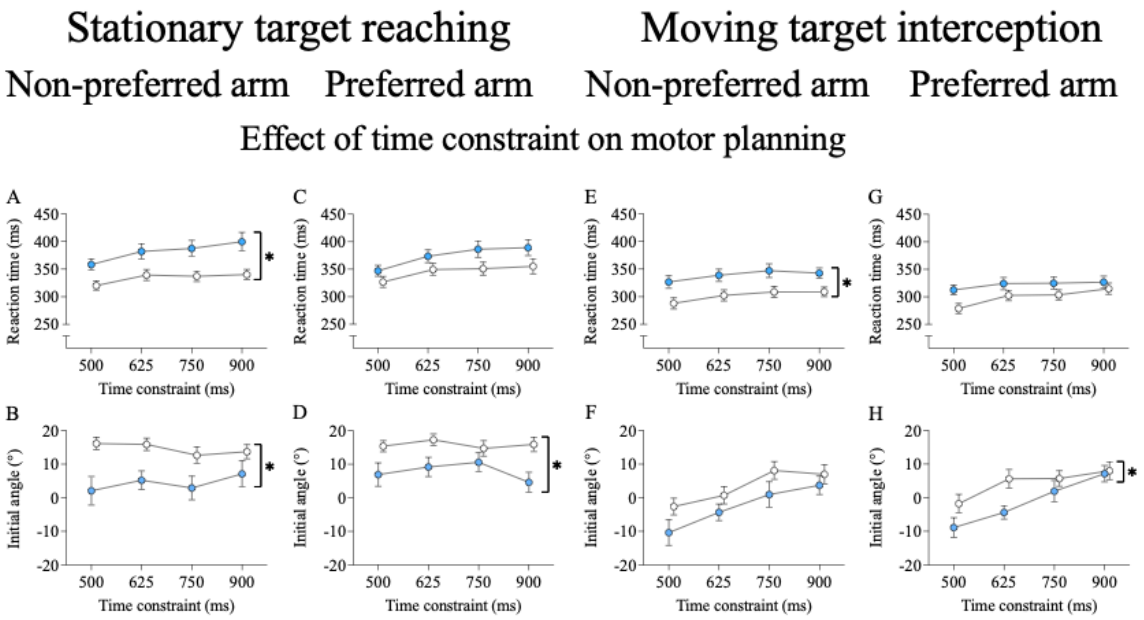

Figure 3.5: Motor planning metrics (reaction time, initial movement angle) across time constraints for stationary target reaching (A-D) and moving target interception (E-H) with each arm in children with cerebral palsy (CP) and typically developing control children (Con). All values are mean ± SE. ✱ group effect.

Motor planning across time constraints

a. Stationary-target reaching

A group effect for reaction time in the non-preferred arm ($p = 0.003$; **Fig. 3.5A**) revealed higher reaction time in children with CP than controls across time constraints (*d range* = 0.589–0.916; all $p < 0.05$). While no group effect was observed in the preferred arm ($p = 0.087$; **Fig. 3.5C**), reaction time in children with CP trended higher than controls across time constraints (*d range* = 0.303–0.526; all $p \geq 0.049$). Group effects for initial movement angle observed in the non-preferred

($p < 0.001$; **Fig. 3.5B**) and preferred arm ($p = 0.005$; **Fig. 3.5D**) indicated lower initial angles in children with CP, with differences most prominent at the 500 and 625 ms time constraint in each arm ($d_{Non\text{-}preferred} = 0.872$ and 0.662, respectively; $d_{Preferred} = 0.606$ and 0.580, respectively; all $p < 0.05$).

b. Moving-target interception

A group effect for reaction time in the non-preferred (p 0.010; **Fig. 3.5E**) revealed children with CP demonstrated higher reaction time than controls across time constraints (*d range* = 0.602–0.688; all $p < 0.05$). Although no group effect was observed in the preferred arm ($p = 0.101$; **Fig. 3.5G**), children with CP exhibited reaction times that trended higher than controls across time constraints, with statistically significant differences observed only at the 500 ms time constraint ($d = 0.613$, $p = 0.021$). While no group effect for initial movement angle was observed in the non-preferred arm (p = 0.070; **Fig. 3.5F**), initial angles trended lower in children with CP than controls across time constraints (*d range* = 0.204–0.480; all $p \geq 0.070$). Conversely, a group effect for initial movement angle in the preferred arm ($p = 0.049$; **Fig. 3.5H**) revealed overall lower initial angles in children with CP than controls, though significant differences were only observed at the 625 ms time constraint ($d = 0.694$, $p = 0.009$).

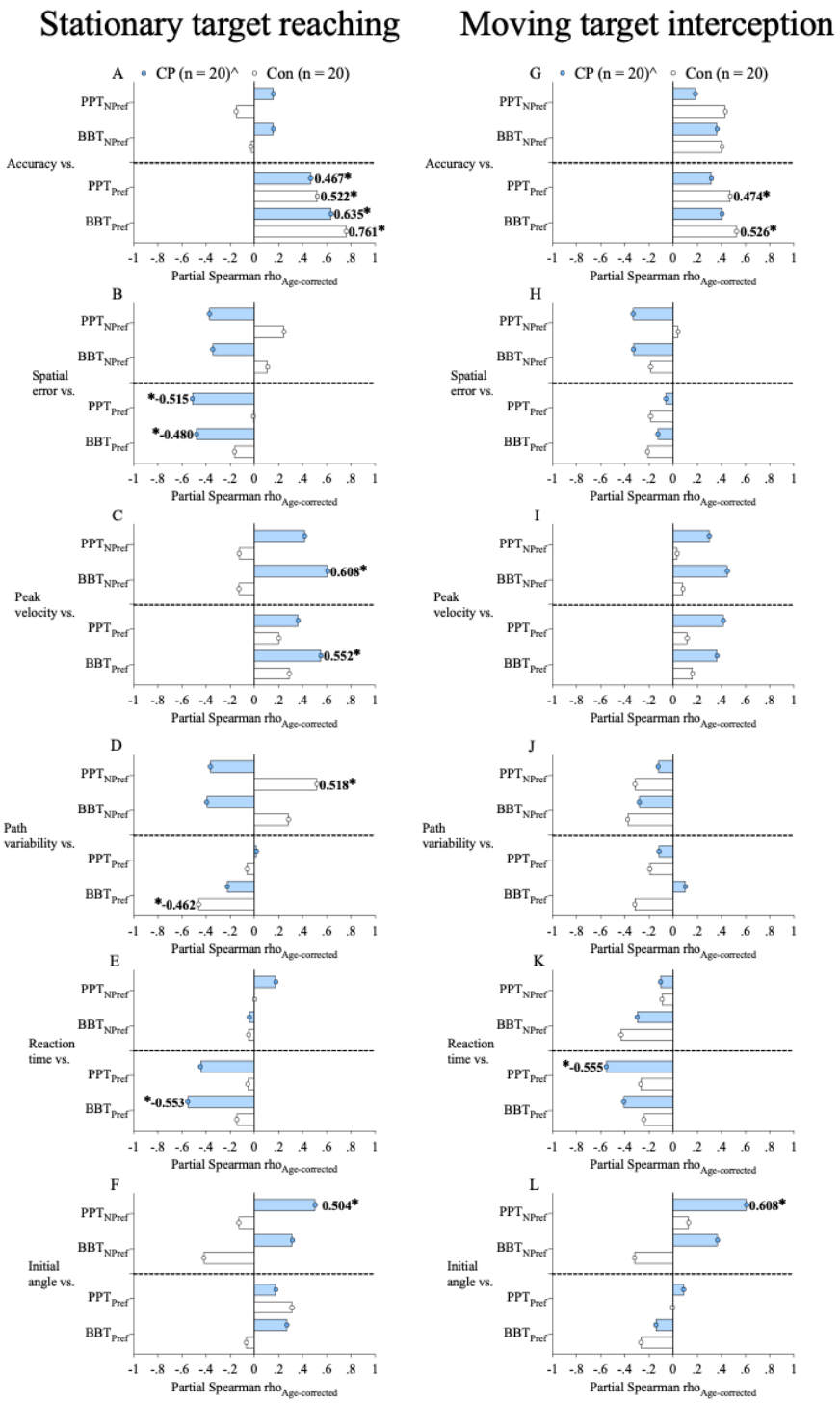

Figure 3.6: Relationships of robotic metrics of motor performance and planning at the highest time constraint during stationary target reaching (A-F) and moving target interception (G-L) with clinical assessment scores on standardized tests of fine manual ability (Purdue Pegboard Test, PPT) and gross manual ability (Box and Blocks Test, BBT) in each arm of children with cerebral palsy (CP) and typically developing control children (Con). Values are age-corrected partial Spearman rho. ^Three participant with CP were unable to complete the PPT with their non-preferred arm (n = 17). *Statistically significant relationships.

Relationship between robotic metrics of motor performance and clinical assessments

Motor performance during the highest time constraint (i.e., 500 ms condition) in stationary target reaching was prominently linked to better clinical scores in children with CP. In the preferred arm, higher accuracy and lower spatial errors were related to higher scores on the BBT and PPT in CP (all $p < 0.05$; **Fig. 3.6A-B**). Higher peak velocity was also related to higher BBT scores in both the preferred and non-preferred arm in CP (all $p < 0.05$; **Fig. 3.6C**). Motor performance during moving target interception was not linked to clinical scores in CP (all $p > 0.05$; **Fig. 3.6G-J**). However, in controls, higher accuracy with the preferred arm during both stationary target reaching and moving target interception was related to higher scores on the BBT and PPT (all $p < 0.05$; **Fig. 3.6A, G)**. Additionally, higher path variability in controls during stationary target reaching (**Fig. 3.6D)** was separately linked to higher PPT scores with the preferred arm, but lower BBT scores with the non-preferred arm (both $p < 0.05$).

Relationship between robotic metrics of motor performance and clinical assessments

Relationships between motor planning metrics and clinical scores in children with CP were task- and arm-specific. In the preferred arm, faster reaction time during stationary target reaching was related to higher BBT scores in those with CP ($p < 0.05$; **Fig. 3.6E**), and faster reaction time during moving target interception was related to higher PPT scores in this group ($p < 0.05$; **Fig. 3.6K**). With the non-preferred arm, higher initial angles during stationary target reaching and moving target interception were separately related to higher PPT scores in children with CP (both $p < 0.05$; **Fig. 3.6F and L**, respectively).

3.4. Discussion

This study revealed significant impairments in motor performance and planning in children with CP compared to typically developing peers during both stationary target reaching and moving target interception tasks. Performance deficits in the CP group included lower accuracy, greater

spatial errors, slower peak velocities, and heightened path variability, and were most pronounced with the non-preferred arm and under stricter time constraints. Planning impairments, characterized by prolonged reaction times and reduced initial movement angles, were also evident in the non-preferred arm but appeared less sensitive to timing restrictions. The magnitude of group differences in both domains were larger during stationary target reaching, suggesting the dynamic context and externally guided visual cues of moving targets may promote increased engagement and/or compensatory adaptive strategies in children with CP, possibly via recruitment of visuoperceptual neural networks. While motor performance generally declined with increased temporal demands, planning deficits in children with CP were less influenced by time constraints, reflecting either the global nature of action planning processes, or a limited capacity to adapt planning strategies under pressure. Importantly, robotic metrics under the most demanding 500 ms time constraint condition were selectively associated with clinical assessments of fine and gross manual ability in both groups, supporting their functional relevance and potential translational utility. Together, these observation reveal task- and limb-specific deficits in motor planning and execution in children with CP, highlighting the clinical potential of robotic assessments to identify therapeutic targets to enhance motor function in this group.

Motor performance deficits in CP are evident across tasks and reaching arm

Children with cerebral palsy (CP) exhibited lower accuracy, higher spatial error, slower peak velocity, and elevated path variability observed during both tasks, in line with previous work detailing higher end-point errors, attenuated reaching velocities, and more inconsistent motor trajectories in this group (289). Deficits were most prominent in the non-preferred arm, aligning with recognized patterns of lateralized motor impairment in spastic CP (464). Notably, group differences in spatial error and peak velocity were also observed in the preferred arm, in line with previous research (289, 463) highlighting bilateral manual ability deficits in CP (120), even in individuals with primarily unilateral affection (474, 475). The robust differences observed during

both tasks indicates that motor execution impairments in CP generalize across conditions requiring both discrete and continuous control. Path variability, a marker of trial-to-trial movement consistency, was elevated even during preferred arm reaching, suggesting that deficits are not linked purely to biomechanical constraints, but reflect centralized impairments in sensorimotor learning and movement adaptation (10, 32). These deficits likely arise from a combination of impaired force generation or weakness (476), dysregulated muscle synergies (477), reduced coordination of joint segments (283), or disturbed attentional regulation under physically demanding task conditions (135). Together, these observations hint at global impairments in motor execution even among children with CP displaying mild-moderate manual impairments (i.e., those at MACS levels I–II (478)), which also serves to highlight the utility of robotic tools in quantifying subclinical performance limitations not readily apparent during clinical assessments.

Motor planning impairments reflect reduced anticipatory control in CP

Prolonged reaction times and diminished initial movement angles across tasks and arms point to anticipatory motor planning deficits in CP, supporting theoretical models (479) and empirical evidence (35) of impaired action planning in this group. Notably, reduced initial movement angles observed particularly in the non-preferred arm suggests children with CP either lack, or more likely underutilize, predictive strategies during trajectory initiation (480), corroborating previous reports of altered motor imagery and strategy-based planning in CP (8). Alternatively, the target pursuit strategy reflected by lower initial angles (272) may arise from demonstrated challenges with visual tracking (260) due to perceptual (112) or visuomotor control deficiencies (481) occurring in isolation, or in combination with action planning deficits. Neurophysiological studies using mobile functional neuroimaging in CP (188) have previously linked prolonged reaction times and planning impairments to altered prefrontal cortex activity (58). These promising observations underscore the need to further explore the role of this central executive region in mediating aberrant cognitive-motor interactions in CP (133).

Differential impact of time constraints on motor performance and planning across task context

Time constraints amplified group differences in both motor execution and planning, with tighter constraints (500, 625 ms) provoking disproportionately greater deficits in accuracy, spatial error, peak velocity, and initial movement angle in children with CP, particularly during stationary reaching. These observations suggest that performance and planning impairments in CP are not fixed, but appear to be modulated by task demands, bolstering claims that environmental factors and functional task contexts can differentially reveal underlying deficits (289, 482), or uncover latent and preserved adaptive capacities (282, 329, 483). Alternately, attenuation of group differences at longer time constraints may have implications for rehabilitation: manipulating task pacing to scaffold diminished planning capacity, or training motor timing via targeted intervention (484) may both promote improved functional outcomes for children with CP.

Interestingly, performance deficits were more pronounced during stationary target reaching than moving target interception, particularly at stricter time constraints. This observation appears counterintuitive, given the heightened cognitive and visuomotor demands of concurrently tracking object motion while concurrently planning, coordinating, and executing precisely timed interceptive reaches to a predicted future target location (28, 272). However, preliminary work in children with unilateral CP noted fewer deficits during rapid interception of moving targets compared to stationary target reaching (289), corroborating additional reports of preserved motor adaptability in children with CP during walk-and-intercept tasks (282). These patterns mirror those reported in individuals with Parkinson's disease, where externally-cued movements guided by visual (485) or auditory stimuli (486) can bypass impaired internal mechanisms of movement initiation (487), enhancing performance by engaging alternate cortical (i.e., premotor) and subcortical (i.e., cerebellar) circuits (488). Consistent with these reports, dynamic tasks with moving targets may elicit greater attention and external cue-driven strategies that either bypass or reduce reliance on impaired internally generated movement commands (270). Moreover, moving

targets may help compensate for anticipatory planning deficits by providing continuous, real-time visual cues that allow for more reactive control. Nonetheless, planning impairments persisted across both tasks, suggesting that while task context modulates performance, core limitations in anticipatory control remain. We speculate that interception performance across time constraints in CP reflects trade-offs between enhanced attentional engagement, scaffolded motor planning from external visuoperceptual cues, and the heightened visuomotor challenge of moving target interception, with time constraints such as target velocity modulating this intricate relationship. These observations support the strategic use of externally guided, time-constrained tasks in rehabilitation to scaffold movement initiation and promote motor control in children with CP. Further, we emphasize that rehabilitation paradigms should consider not just task difficulty, but also the types of cues and engagement elicited by different interventional protocols (124) to optimize functional outcomes.

Robotic metrics linked to functional manual abilities

Robotic measures obtained under high temporal demands, especially accuracy, spatial error, reaction time, and initial movement angle, were directly and moderately related to performance on standardized assessments of gross and fine manual ability in children with CP. These relationships were strongest in the preferred arm displaying more preserved motor control and higher task completion rates, supporting the potential of robotic metrics as sensitive proxies for real-world motor function, especially when collected under challenging time restrictions that better reflect the temporal demands of many real-world movements. Importantly, planning-related measures (i.e., reaction time, initial angle) were also related to clinical scores, providing support for expanding clinical evaluation beyond endpoint accuracy. Given that conventional clinical assessments often demonstrate strong ceiling effects with scores plateauing in high-functioning children, robotic assessments may serve as sensitive tools for capturing residual deficits and tracking therapeutic gains in both research and clinical settings. The lack of significant associations

for interception task metrics highlights a key limitation of existing clinical behavioral assessments: no current evaluation uses moving objects or requires interceptive behaviors commonly performed in daily life, which limits the ecological validity of these tests. This paucity underscores the need for novel, game-based clinical assessments with moving targets that challenge the sensorimotor systems while concurrently recruiting latent visuoperceptual networks to improve attentional engagement in young children.

3.5. Limitations

Limitations of the study design require acknowledgement. First, the study sample comprised children with spastic CP displaying mild-moderate manual impairments (i.e., MACS levels I–II), limiting generalizability to children with more severe manual impairments. Although this approach reduced variability and ensured task compliance and high completion rates, future work should include children with greater functional limitations who may exhibit distinct motor profiles. Second, information on sensory, perceptual, visuomotor, and cognitive abilities was lacking, and we lacked access to brain scans or neurophysiological data (e.g., transcranial magnetic stimulation-based corticospinal tract connectivity (142)) that could improve categorization of participants with CP. Although planning deficits were discussed in relation to cortical systems known to be altered in CP, such as the prefrontal and sensorimotor cortices, no neuroimaging or electrophysiological data were collected to confirm these associations. Future studies incorporating mobile functional near-infrared spectroscopy or MRI-based imaging may clarify the neural correlates of the observed planning impairments to strengthen interpretation of brain–behavior relationships. Third, while the use of bilateral testing is a strength of the study, the large proportion of right-hand dominant controls compared to more variable hand preference in the CP group may have introduced asymmetries unrelated to impairment severity. Future work could include neuroimaging-based motor dominance or lesion mapping to more precisely stratify participants by hemispheric involvement. Fourth, aspects of our task protocol (e.g., fixed task order with the

reaching task preceding the interception task, and the preferred arm tested ahead of the non-preferred arm) may have introduced either fatigue or practice effects that differentially impacted task performance across groups. Although the task order and amount of practice (10 trials) was consistent across all study participants, the counterbalancing of tasks and arm was limited by feasibility constraints in this pediatric population. Future designs should attempt to randomize task order, or include more practice trials to better account for potentially differential learning and engagement effects. Despite these limitations, the study provides details how children with CP plan and execute movements under varying temporal and task demands, offering a foundation for future translational and interventional research.

3.6. Conclusion

This study provides compelling evidence that children with CP exhibit significant impairments in motor execution and planning which are especially pronounced under strict time constraints. Robotic tasks revealed that these deficits vary by task demands and limb, with planning impairments emerging as robust markers of upper limb dysfunction. Importantly, these metrics were linked to standardized clinical assessments, reinforcing their real-world relevance. By integrating dynamic, time-constrained tasks, robotic assessments offer a powerful complement to clinical tools, enabling more precise identification of individualized therapeutic targets to guide personalized rehabilitation in CP.

CHAPTER 4

ACCURACY DEFICITS DURING ROBOTIC TIME-CONSTRAINED REACHING ARE RELATED TO ALTERED PREFRONTAL CORTEX ACTIVITY IN CHILDREN WITH CEREBRAL PALSY

[1] Khan, O.A., Singh, T., Barany, D., Modlesky, C.M. 2024. *Journal of Neuroengineering & Rehabilitation*, 21(1): 216. https://doi.org/10.1186/s12984-024-01502-x

Abstract

Background: The prefrontal cortex (PFC) is an important node for action planning in the frontoparietal reaching network but its role in reaching in children with cerebral palsy (CP) is unexplored. This case–control study combines a robotic task with functional near-infrared spectroscopy (fNIRS) to concurrently assess reaching accuracy and PFC activity during time-constrained, goal- directed reaching in children with CP. We hypothesized that reaching accuracy in children with CP would be lower than in typically developing children and would be related to PFC activity.

Methods: Fourteen children with spastic CP (5–11 y; Manual Ability Classification System level I-II) and 14 age-, sex- and arm dominance-matched typically developing controls performed seated uniplanar reaches with a robotic arm (KINARM End-Point Lab) to hit visual targets projected onto a screen. Four blocks of 10 reaching trials each were performed for each arm. Time constraint (high, low) was varied across blocks by changing the time participants had to hit the target.

Results: Children with CP displayed lower reaching accuracy compared to controls, with greater deficits observed in the non-preferred arm ($d = 1.916$, $p < 0.001$) than the preferred arm ($d = 1.033$, $p = 0.011$). Inter-limb differences in accuracy were observed only in children with CP ($d = 0.839$, $p < 0.001$). PFC activity differed across groups during preferred arm reaching, with PFC deactivation observed in children with CP under high time constraints compared to PFC activation in controls ($d = 1.086$, $p = 0.006$). Children with CP also exhibited lower PFC activity under high time constraint compared to low time constraint in the preferred arm ($d = 0.702$, $p = 0.001$). PFC activity was positively related to reaching accuracy across time constraints in both arms in children with CP, but not in controls.

Conclusion: Contrasting patterns of PFC activity observed in children with CP compared to age- and sex-matched controls during a robotic reaching task lends support for the concurrent use of fNIRS and robotics to assess goal-directed reaching in CP.

Trial Registration: Data collected as part of a larger randomized controlled trial (NCT03484078)

4.1. Background

Goal-directed reaching is a fundamental motor behavior that empowers children to build relationships, participate in play and sport and achieve functional independence in activities of daily living. Successful reaching requires the rapid and continuous coordination of the visual, sensorimotor, and attentional-perceptual neural systems (261). This multi-system integration is especially challenging for children with neurodevelopmental disorders such as cerebral palsy (CP) (69, 136). Affecting 1 in 323 children in the United States, CP is considered the most common cause of childhood-onset motor disability (489). Children with CP exhibit central deficits in action planning (8, 10), visuospatial attention (9), eye-hand coordination (30, 177), and sensorimotor function (178, 490), all of which contribute to the impaired reaching behaviors observed in these children (121). Understanding the neural correlates of these impairments is essential to developing targeted interventions to improve upper limb function in children with CP.

Robotic technologies have recently emerged as valid and reliable tools to assess the complex multi-system deficits observed in children with CP (13-18, 21, 22). In addition to providing objective quantitative measures of movement dysfunction, robotic assessments can incorporate reliable, sensitive, and ecologically valid tasks that better translate to real-world performance (491) than subjective clinical assessments of manual abilities (11, 492). Robotic technologies are safe, feasible, and well tolerated by young children with neurological impairments, and have been used to quantify upper limb sensorimotor (13, 14, 17, 18), visuospatial (21), and executive functions (22) in children with perinatal stroke-induced CP. In line with previous reaching studies using motion capture techniques (6, 26), robot-derived reaching metrics revealed global deficits in reaching kinematics of children with arterial stroke-induced CP that were related to clinical metrics of manual ability (14). The integration of neuroimaging and neurophysiological assessments alongside standardized robotic tasks can help researchers evaluate brain-behavior relationships in both neurotypical children and children with neurodevelopmental disorders like CP. Prior work combining robotic assessment of reaching with neuroimaging revealed sensory

deficits were associated with sensory tract development in children with perinatal stroke (15), highlighting the importance of assessing neurophysiological outcomes alongside robot-derived metrics to better understand the reaching deficits observed in CP.

Despite the promise of more sensitive assessments offered by integrated robotics-neuroimaging, the use of functional neuroimaging has been limited in children with CP due to their inability to stay still while remaining attentive and engaged throughout the assessment task. The recent emergence of portable, non-invasive neuroimaging technologies like functional near-infrared spectroscopy (fNIRS) shows promise in overcoming this limitation (40). Source optodes on fNIRS devices emit specific wavelengths of near-infrared light that pass through the skin and superficial tissue and are differentially absorbed by oxygenated and deoxygenated hemoglobin within the outer 5-10 mm strip of cortical grey matter underlying the surface optodes. Light waves re-emerge and are captured by detector optodes located at specific distances from the source optode. The light intensity differential indicates relative changes in hemoglobin concentrations that serve as indirect indices of neural activity in the underlying cortical regions spanning the source-detector channel (38). Advantages of fNIRS include its portability, relative inexpensiveness, and robustness to motion artifacts compared to functional magnetic resonance imaging, and superior comfort, higher spatial resolution, and ease of application compared to electroencephalography (37). These characteristics make fNIRS a promising tool for assessing task-induced cortical activity in adults (493) and children with neurological impairments (40).

In contrast to these stated advantages, the fNIRS literature in CP is sparse. Most prior studies assessed sensorimotor cortex activation during simple single- and multi-joint movements (41-49). An exploratory study reported increased activation in the prefrontal cortex (PFC) of two adults with CP during an upper limb aiming (ball-drop) task (352). The PFC is an important node for action planning and prediction within the fronto-parietal neural network for goal-directed reaching (247, 248), priming the sensorimotor cortices for the expected sensorimotor inputs arising from novel and purposeful movements (300). The PFC is considered a cortical hub for mediating

visuospatial attention (494) and spatial localization (55) abilities essential for accurate targeted reaching (28). While prior studies have evaluated PFC activation during reaching tasks in neurotypical adults (55, 495), the exploration of PFC activity in children with CP has been limited to motor planning and cognitive-motor dual-tasks (57-59). The heightened PFC activity observed in children with CP during these dual-tasks was posited to represent neural resource re-allocation to compensate for their impaired posture and balance (58). Interestingly, PFC activity diminished to levels comparable with typically developing controls following intensive training, suggesting PFC activity optimization may precede, accompany, or follow the improved functional abilities seen in children with CP post-intervention (59). In contrast to the increased PFC activation observed in upper limb tasks, a recent fNIRS study reported lowered PFC activity in young children with CP during robot-assisted walking (56). The increased PFC activity observed in these children following robot-assisted gait training was associated with improvements in functional mobility. These initial studies suggest that PFC activity may either serve as a potential neurophysiological marker for post-intervention functional gains, or more speculatively, be a relative therapeutic target in children with CP. Despite these promising preliminary observations, to the best of our knowledge, no study has determined PFC activity during goal-directed reaching in children with CP.

This study aimed to concurrently evaluate reaching accuracy and PFC activity in children with CP using a robotic goal-directed reaching task that incorporated distinct time constraints. We aimed to [1] determine if children with CP have deficits in reaching accuracy and a different level of task-evoked PFC activity compared to typically developing children, and [2] determine if reaching accuracy is related to PFC activity across differing time constraints. Based on the prior literature and studies summarized above (14, 16, 21, 55-59, 352, 495), we hypothesized that [1] children with CP would exhibit lower reaching accuracy and higher PFC activity during the time-constrained reaching task than typically developing children, and [2] that PFC activation would be positively related to reaching accuracy in children with CP.

4.2. Methods

4.2.1. Participants

Children with spastic CP aged 5–11 years were recruited from schools, social media platforms, pediatric rehabilitation centers, Children's Healthcare of Atlanta and the Cerebral Palsy Foundation as part of a larger randomized controlled trial. Age- (± 1.5 y) and sex-matched typically developing children with no known neurological disorders and height and body mass between the 5th to 95th age- and sex-based percentiles were recruited as controls. Exclusion criteria for this study were [1] Manual Ability Classification System level V (does not handle objects and has severely limited ability to perform simple actions), [2] cognitive impairments that impairs the ability to follow simple verbal instructions, [3] botulinum toxin injection in the past 6 months, and [4] significant visual acuity problems and/or upper limb musculoskeletal deformities that would preclude completion of testing. The Institutional Review Board at the University of Georgia approved this study. Prior to the study, written informed consent was obtained from the participants' parent or legal guardian, and informed assent was obtained from the participant.

4.2.2. Anthropometrics

Height and body mass were assessed while participants wore minimal clothing and were in bare feet. Height was measured using a stadiometer (Seca 217; Seca GmbH & Co. KG., Germany) to the nearest 0.1 cm, and body mass was measured using a digital scale (Detecto 6550, Cardinal Scale, MO, USA) to the nearest 0.1 kg. Body mass index (BMI) was calculated using height and body mass. Normative data published by the US Centers for Disease Control and Prevention (467) were used to determine age- and sex-based percentiles for body mass, height and BMI. Hand preference was assessed using the Edinburgh Handedness Inventory-Short Form (468) to confirm right-arm preference for all participants.

4.2.3. Clinical measures

Manual ability was classified by the parent/guardian using the Manual Ability Classification System (MACS) (221). Gross motor function was assessed using the Gross Motor

Function Classification System (GMFCS) (469). Muscle tone was assessed using the Hypertonia Assessment Tool (HAT) (470).

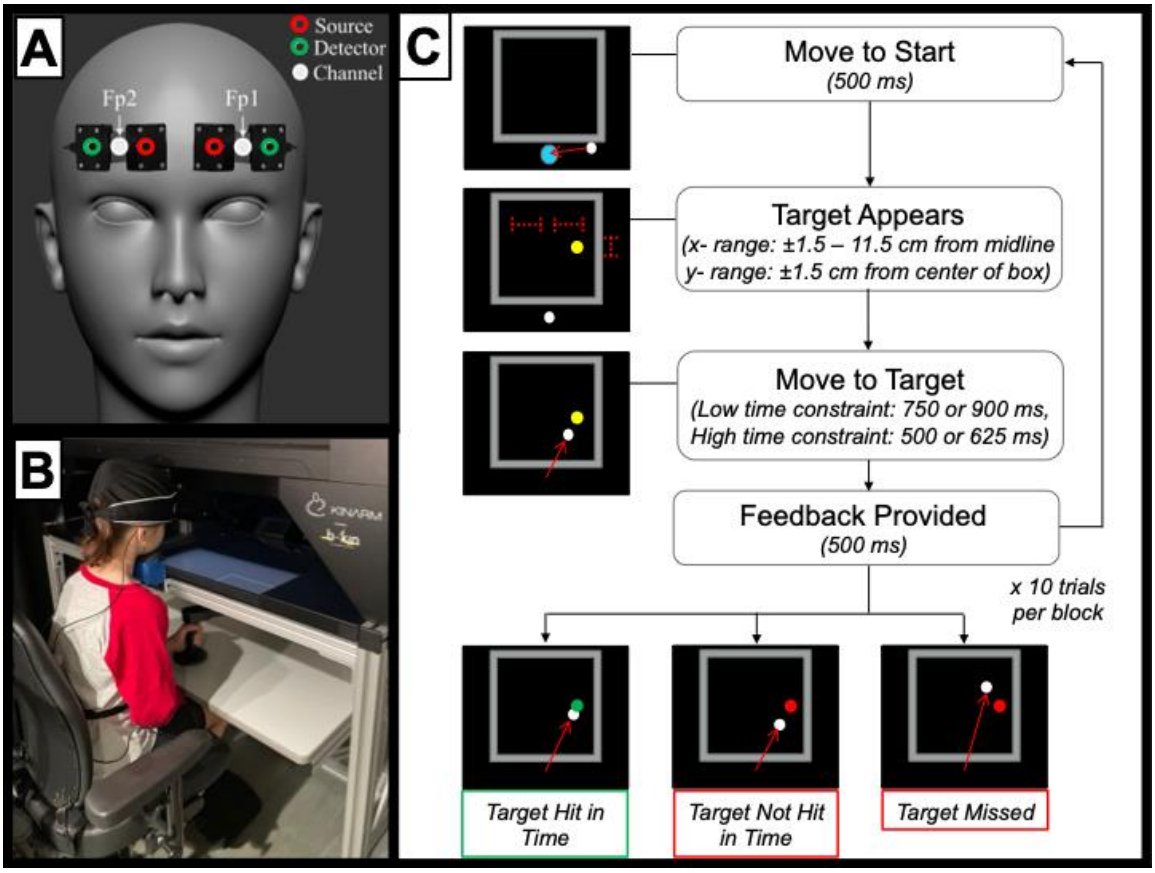

Figure 4.1. Study methods. (A) Functional near-infrared spectroscopy (fNIRS) device placement over the regions of interest in the left PFC (Fp1) and right PFC (Fp2), based on the International 10/20 system. (B) Experimental setup with the participant positioned within the KINARM robotic device. (C) Trial protocol for the robotic time-constrained reaching task.

4.2.4. Functional neuroimaging (fNIRS) setup

Two lightweight, portable (Bluetooth-enabled) fNIRS devices (Portalite, Artinis Medical Systems, The Netherlands) were secured to the participant's forehead, as depicted in **Figure 4.1 (A).** The device has 3 optodes (sources) set at fixed distances of 3, 3.5, and 4 cm from a single fixed 'detector', yielding three spatially overlapping source-detector channels. Near-infrared light at two wavelengths (850 nm, 760 nm) was emitted from the source optodes, with devices centered over the Fp1 and Fp2 locations of the International 10-20 system to cover the bilateral prefrontal

cortices. Data from the 3 cm channel were used for further analysis, in line with manufacturer recommendations and previous studies that used the same device in typically developing children (496). To minimize interference from ambient light, a black felt cloth was placed over the fNIRS devices and secured with a black cap. Data were sampled at 50 Hz and visualized in real-time with the manufacturer's data recording software (Oxysoft v3.2.64x64, Artinis).

4.2.5. Experimental setup

The general experimental setup was adapted for children from a previous study (266) and is illustrated in **Figure 4.1 (B).** Briefly, participants sat on a height-adjustable chair with their feet supported on an adjustable footrest. They used one hand to grasp the handle of a robotic device (KINARM End-Point Laboratory, Ontario, Canada). Handle movement in the horizontal plane controlled the position of a cursor (white circle, 1 cm diameter) on a screen comprised of a semi-transparent mirror. All visual stimuli were projected onto this screen at 60 Hz or 120 Hz from a monitor at the top of the workspace to ensure the cursor and visual stimuli were on the same horizontal plane. Participants could track the location of the cursor on-screen during the reaching movements, but they could not see the physical movements of the arm during the movements (i.e., no direct visual feedback) as the hand was occluded from direct sight by the screen. Handle position and velocity of movement was recorded at 1000 Hz. To minimize head motion, participants were instructed to stabilize their chin on a fixed chinrest with the crown of their head against the KINARM workspace boundary, and to fix their gaze on the cursor and target for the entire task.

The trial protocol is summarized in **Figure 4.1 (C).** Briefly, each trial began with the participants moving the cursor to a start position (2 cm blue circle) in the midline of the visual display (x = 0) directly below the workspace (34 by 34 cm box centered on the midline). If the cursor position was maintained for 500 ms, the start position disappeared, and the target (yellow circle, 1 cm diameter) appeared onscreen. The target location on each trial was randomized, with targets appearing on the left or right side of the workspace at equal probability. The x-position of the target was constrained within a uniform distribution around a mean position ± 6.5 cm from the

workspace mid-line (range ± 5 cm). The y-position of the target was constrained within a uniform distribution around the center of the workspace (mean position 19 cm from the start position, range ± 3 cm). Participants were instructed to move the cursor to hit the target as rapidly and accurately as possible for every trial. They were not required to stop at the target location. A "hit" was recorded when the cursor first overlapped with the target. Performance feedback was provided for 500 ms once the object was hit or the maximum trial duration was reached. If the target was hit within the block-specific time constraint, it would turn green ("hit"); if the target was missed or hit after the time constraint period, it would turn red ("miss"). A 2000 ms delay was incorporated between successive trials.

Targets remained onscreen for a maximum of 500 ms or 625 ms for the high time constraint blocks, and 750 ms or 900 ms for the low time constraint blocks. Before and after each block, participants were instructed to let go of the handle and look at the cursor onscreen for 25-30 s (randomized) to allow PFC hemodynamics to return to baseline levels. The preferred (right) arm was always assessed first, with 4 blocks performed with each arm and the block order randomized within each arm. Each block comprised 10 trials (80 trials total), with a time constraint defined and maintained for all trials within a block.

4.2.6. fNIRS data processing

All fNIRS data were preprocessed in MATLAB® (MathWorks, Natick, MA, USA) using the HOMER3 (v1.28.1) software package (436). Current best practices for fNIRS data processing were followed (402). First, frequency distributions of all channels and both wavelengths were visually inspected with power spectral density graphs to detect the characteristic hemodynamic 'pulse' at 1-2 Hz that signifies good signal quality. Raw light intensity signals were subsequently converted into changes in optical density (*Intensity2OD* function) and submitted through a low-pass filter (*BandpassFilt* function with parameters *hpf* = 0 Hz, *lpf* = 0.09 Hz) to account for components from systemic physiology (e.g., cardiac pulsations, respiratory cycles). The filtered time series data were then corrected for motion artifacts using the hybrid spline interpolation-

Savitzky Golay procedure (*MotionCorrectSplineSG* function with parameters $p = 0.99$, *FrameSize* = 10 sec) chosen for its efficiency and effectiveness in accounting for both baseline shifts (via spline interpolation) and sharp motion artifacts (via robust, locally weighted smoothing through the Savitzky-Golay filter) (441). Motion-corrected optical density data were converted into relative changes in hemoglobin concentration using the modified Beer-Lambert law (*OD2Conc* function with parameters *ppf* = 1, 1). Data were then baseline corrected by subtracting the mean of the signal from the 2 seconds preceding each trial and block averages for changes in hemoglobin concentration were calculated for each block (*BlockAvg* function with parameters *trange* = -2 to 45 sec). Baseline-corrected time-series block averages were exported and mean values were calculated for a time period spanning 0 to 45 seconds post-trial onset. We used mean changes in concentration of oxyhemoglobin (∂HbO) as a marker of brain activation as oxyhemoglobin has previously been shown to be a more sensitive indicator of neural activity in the PFC than deoxyhemoglobin (497, 498) and has been the chromophore of choice to assess PFC activity in children with CP (57-59).

4.2.7. Statistical analysis

Statistical analyses were conducted in RStudio (v2022.07.2, R Core Team 2022) and SPSS (v27.0.1, IBM Corp., Armonk, NY). Data were examined for normality by assessing skewness and kurtosis values and using the Shapiro—Wilk test. Group differences in physical characteristics were assessed using independent t-tests for normally distributed data and with Mann—Whitney *U* tests for non-normally distributed data. One-sample t-tests were used to assess if height, body mass, and BMI percentiles differed from 50th percentiles for age- and sex-based norms. Linear mixed-effect models were used for the performance outcome (reaching accuracy) with fixed effects of group (CP vs controls), arm (preferred vs non-preferred), time constraint (high vs low) nested within subject (random effect). Linear mixed-effect models were also used for the fNIRS outcome (Change in HbO) with the addition of PFC hemisphere (ipsilateral vs contralateral) as a fixed effect, as these statistical models can account for the inherently nested structure of fNIRS data (437) and the correlations arising from repeated measurements (499). Pairwise comparisons were conducted

for significant interactions and main effects. Alpha was set at 0.05 a priori and a multiple comparison correction was conducted using the Benjamini-Hochberg procedure (500). The relationship between reaching accuracy and PFC activity was assessed using Spearman rank correlation (r_s). Effect sizes were determined using Cohen's d (d), with 0.2, 0.5 and 0.8 representing small, medium, and large effect sizes, respectively (473). Data are presented as mean ± SD in the text and tables and as mean ± SE in figures, unless specified otherwise.

4.3. Results

4.3.1. Participant characteristics

Fourteen children with spastic CP and fourteen age- and sex-matched typically developing control children met the criteria for participation in the study. Participant characteristics are presented in **Table 4.1**. No between-group differences were detected for any physical characteristic (all $p > 0.05$) and percentiles for height, body mass and BMI were not different from the 50th age- and sex-based percentiles for either group (all $p > 0.05$).

4.3.2. Reaching accuracy

The effect of group, reaching arm, and time constraint on reaching accuracy is illustrated in **Figure 4.2**. A significant group-by-arm interaction was observed for reaching accuracy ($p < 0.001$; **Fig. 4.2 (A)**). Post-hoc tests indicated that children with CP were less accurate than controls with both arms, but the accuracy deficits were twice as large with the non-preferred arm (mean difference = -32 ± 6 %, $d = 1.916$, $p < 0.001$) than the preferred arm (mean difference = -16 ± 6 %, $d = 1.033$, $p = 0.011$). Inter-limb differences in accuracy were observed in children with CP, with lower accuracy noted with the non-preferred arm (mean difference = -14 ± 17 %, $d = 0.839$, $p = 0.008$). In contrast, no inter-limb differences in accuracy were observed in controls ($d = 0.170$, $p > 0.05$). A significant main effect of time constraint was observed with both the non-preferred arm ($p = 0.012$; **Fig. 4.2 (B)**) and the preferred arm ($p < 0.001$; **Fig. 4.2 (C)**).

Table 4.1. Physical characteristics of children with cerebral palsy (CP) and typically developing controls (Con).

	CP (n = 14)	Con (n = 14)	*d*	*p*
Age (years)	8.7 ± 1.7	8.6 ± 1.9	0.094	0.815
Sex (male/female)	9/5	9/5	—	—
Height (m)	1.30 ± 0.13	1.32 ± 0.11	0.167	0.927
Height (%)	38 ± 34	59 ± 25	0.677	0.073
Body mass (kg)	30.6 ± 7.7	29.7 ± 9.0	0.110	0.520
Body mass (%)	58 ± 30	55 ± 28	0.074	0.846
Body mass index	18.0 ± 3.4	16.7 ± 2.4	0.469	0.233
Body mass index (%)	60 ± 34	54 ± 29	0.195	0.370
Arm dominance (right/left)	14/0	14/0	—	—
CP diagnosis (unilateral/bilateral)	3/11	—	—	—
GMFCS level (I/II)	11/3	—	—	—
MACS level (I/II)	4/10	—	—	—
Hypertonia Assessment Tool (right arm)	$11^a/2^b/0^c/1^d$	$14^a/0^b/0^c/0^d$	—	—
Hypertonia Assessment Tool (left arm)	$8^a/5^b/0^c/1^d$	$14^a/0^b/0^c/0^d$	—	—

All values are mean ± SD. % represents percentiles for height, body mass, and body mass index, none of which were significantly different from the age- and sex-based 50th percentiles. Gross motor function indicated by the Gross Motor Function Classification System (GMFCS) rating. Manual ability indicated by the Manual Ability Classification System (MACS) rating. Muscle tone abnormality indicated by the Hypertonia Assessment Tool (HAT) rating as ^{a}normal tone, ^{b}spasticity, ^{c}dystonia, ^{d}mixed tone (spasticity and dystonia).

4.3.3. PFC activity

Effects of group, arm, and time constraint on overall PFC activity are also visualized in **Figure 4.2**. There were no group or arm effects on overall PFC activity (both $p > 0.05$; **Fig. 4.2 (D)**). There were no group or time constraint effects on PFC activity when reaching with the non-preferred arm (both $p > 0.05$; **Fig. 4.2 (E)**). A significant group-by-time constraint interaction was noted for overall PFC activity only during preferred arm reaching ($p = 0.001$; **Fig. 4.2 (F)**). Post-hoc tests showed that children with CP had lower PFC activity than controls when reaching under high time constraints (mean difference = -100.5 ± 35.4 M.mm, $d = 1.086$, $p = 0.008$), with no group differences observed under low time constraints ($d = 0.003$, $p = 0.994$). Children with CP also exhibited lower PFC activity under high time constraints compared to low time constraint reaching (mean difference = 73.2 ± 40.4 M.mm, $d = 0.702$, $p = 0.021$). This within-group difference was not observed in controls ($d = 0.295$, $p = 0.290$).

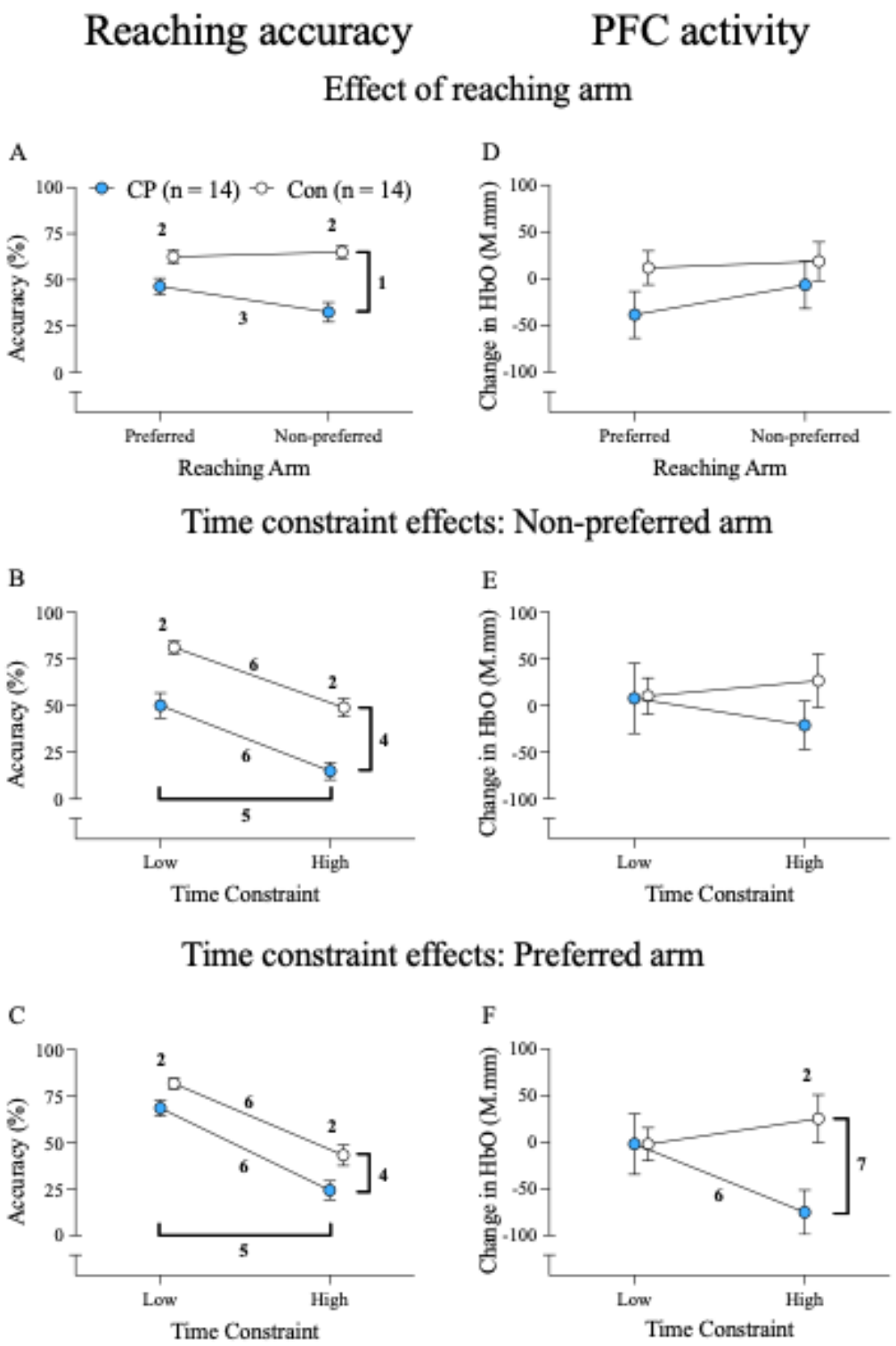

Figure 4.2. Reaching accuracy and overall PFC activity (averaged across hemispheres) for time-constrained reaching. Results are presented for each arm (**A** and **D**), and for each time constraint during non-preferred arm (**B** and **E**) and preferred arm reaching (**C** and **F**). Values are mean ± SE; [1]group x arm interaction; [2]group difference; [3]arm difference; [4]main effect of group; [5]main effect of time constraint; [6]time constraint difference; [7]group x time constraint interaction; *HbO* oxyhemoglobin, *CP* Cerebral palsy, *Con* Typically developing controls, r_s Spearman rho.

4.3.4. Relationship between reaching accuracy and overall PFC activity

Relationships between reaching accuracy and average PFC activity are presented in **Figure 4.3**. For reaching done under low time constraints, positive relationships were observed only in the children with CP, with strong relationships noted for the non-preferred arm and the preferred arm (both $p < 0.05$; **Fig 4.3 (A-B)**). For high time constraint reaching, a strong positive relationship was observed in children with CP with the non-preferred arm ($p = 0.004$; **Fig. 4.3 (C)**), but a significant relationship was not detected with the preferred arm ($p > 0.05$; **Fig. 4.3 (D)**). Interestingly, these relationships consistently trended in the opposite (i.e., negative) direction for controls across time constraints in both arms, with a significant negative relationship noted only under low time constraints during preferred arm reaching ($p = 0.045$; **Fig. 4.3 (B)**).

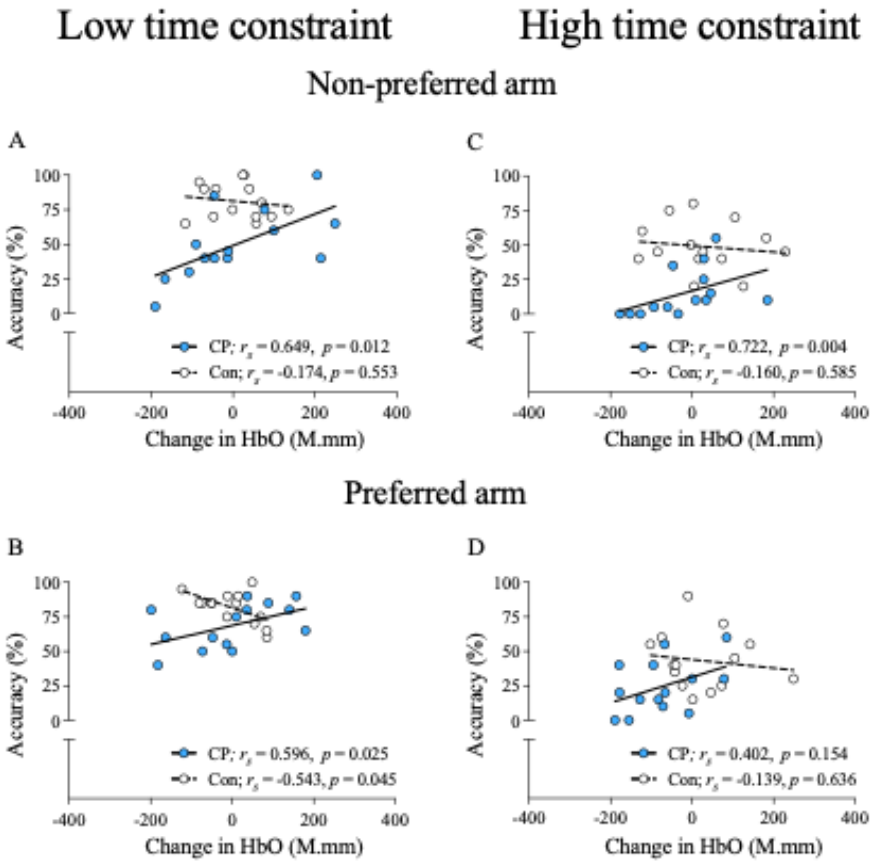

Figure 4.3. Relationships between overall PFC activity and reaching accuracy. Relationships of overall PFC activity with reaching accuracy for low time constraint (**A**, **B**) and high time constraint (**C**, **D**) reaching with the non-preferred arm (**A**, **C**) and the preferred arm (**B**, **D**) are illustrated. *PFC* Prefrontal cortex, *LTC* Low time constraint, *HTC* High time constraint, *HbO* oxyhemoglobin, *CP* Cerebral palsy, *Con* Typically developing controls, r_s Spearman rho.

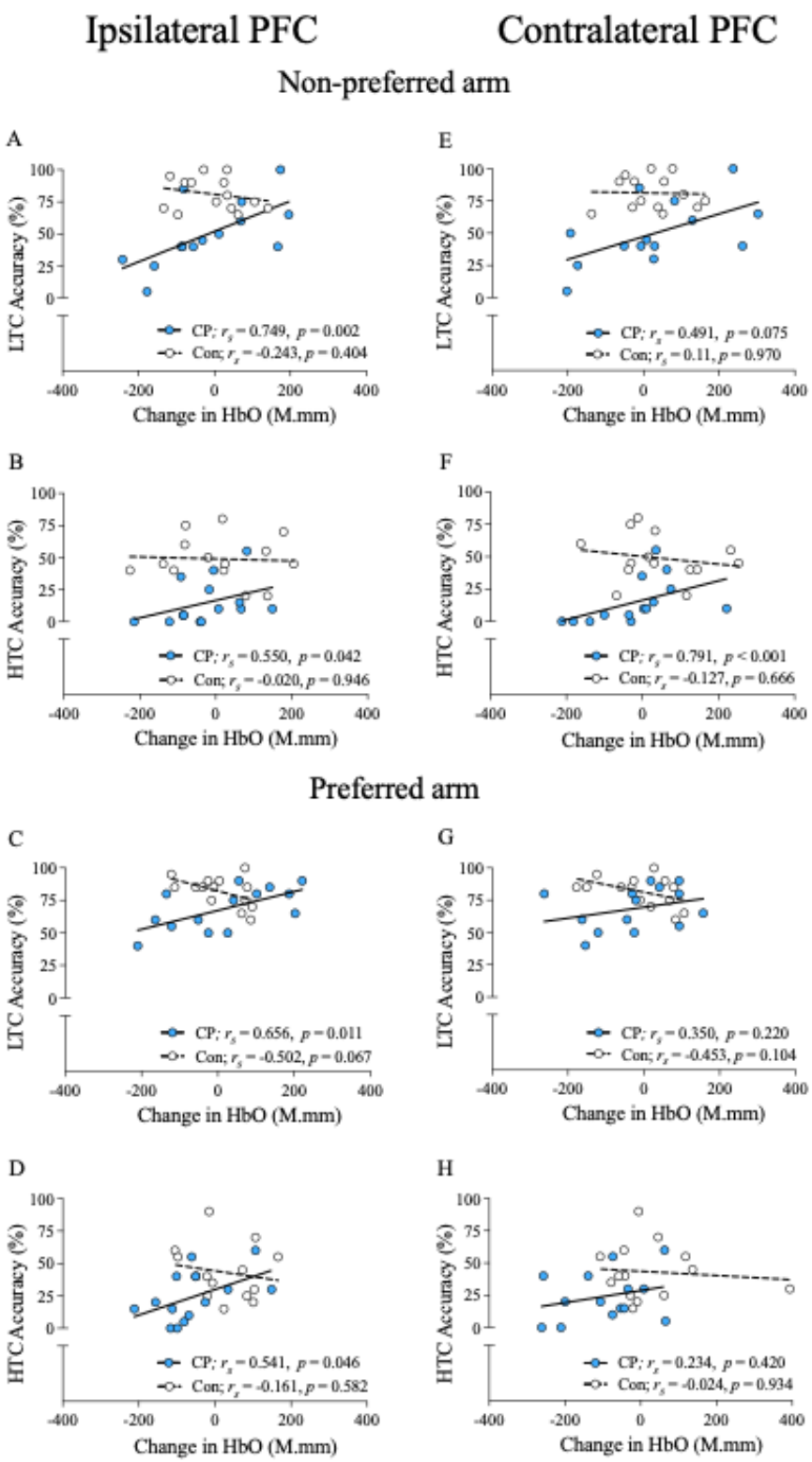

Figure 4.4. Relationships between hemispheric PFC activity and reaching accuracy. Relationships of ipsilateral PFC (**A**–**D**) and contralateral PFC (**E**–**H**) activity with reaching accuracy for preferred arm (**C**, **D**, **G**, **H**) and non-preferred arm (**A**, **B**, **E**, **F**) reaching are illustrated for the low and high time constraint conditions. *PFC* Prefrontal cortex, *LTC* Low time constraint, *HTC* High time constraint, *HbO* oxyhemoglobin, *CP* Cerebral palsy, *Con* Typically developing controls, r_s Spearman rho.

4.3.5. Relationship between reaching accuracy and ipsilateral PFC activity

Relationships between reaching accuracy and ipsilateral PFC activity are depicted in **Figure 4.4**. Strong positive relationships were detected in children with CP when reaching under low time constraints with both the non-preferred arm and the preferred arm (both $p < 0.05$; **Fig. 4.4 (A and C)**). Moderate positive relationships were observed in children with CP under high time constraints with both the non-preferred arm and the preferred arm (both $p < 0.05$; **Fig. 4.4 (B and D)**). No significant relationships were observed in controls (all $p > 0.05$).

4.3.6. Relationship between reaching accuracy and contralateral PFC activity

Figure 4.4 also depicts relationships between reaching accuracy and contralateral PFC activity. A strong positive relationship was noted in children with CP when reaching under high time constraints with the non-preferred arm ($p < 0.001$; **Fig. 4.4 (F)**), but not with the preferred arm ($p > 0.05$; **Fig. 4.4 (H)**). Similarly positive but non-significant trends were noted for children with CP with low time constraint reaching with either arm (both $p > 0.05$; **Fig. 4.4 (E and G)**). None of these relationships were significant for controls (all $p > 0.05$).

4.4. Discussion

In this study, we examined reaching accuracy and PFC activation during a time-constrained reaching task across both upper limbs in children with CP. As hypothesized, children with CP exhibited deficits in visuomotor accuracy compared to age-, sex-, and arm dominance-matched typically developing controls, with deficits accentuated when reaching with the non-preferred arm. Interestingly, imposing high time constraints adversely impacted reaching accuracy to a similar degree in both children with CP and typically developing controls, regardless of the arm used for reaching. Group differences in overall PFC activity were noted only when reaching with the preferred arm. Contrary to expectation, children with CP displayed PFC deactivation under high time constraints compared to low time constraints, while typically developing controls showed the opposite but non-significant trend of increased PFC activation. Moderate-to-strong positive

relationships between overall PFC activity and reaching accuracy were observed in children with CP, both when reaching under low time constraints (for each arm) and under high time constraints (for non-preferred arm only). Correlation analyses suggested distinct roles of each PFC hemisphere during time-constrained reaching in children with CP. Specifically, there were strong positive relationships between the ipsilateral PFC activity and accuracy when reaching under low time constraints for both arms. In contrast, contralateral PFC activity was positively related to accuracy only when reaching under high time constraints with the non-preferred arm. No significant relationship between PFC activity and accuracy was observed with controls. Overall, these novel findings suggest that reaching performance and PFC activity in children with CP depends on both imposed time constraints and the arm used for reaching.

4.4.1. Reaching accuracy

The pronounced inter-limb differences in reaching accuracy observed in children with CP is in line with previous studies (289) that report similar deficits in children with CP during time-constrained reaching with the non-preferred arm. Children with spastic CP have recognized motor control deficits that hinder reaching performance, with slower, less flexible and more fragmented movements observed in the non-preferred arm (289, 501). Time-constrained reaching places increased demands on the neuromuscular system that contribute to markedly different movement strategies for each arm during reaching in CP (283). As in previous studies, we did not observe inter-limb differences in reaching accuracy in controls, indicating that accuracy deficits were specific to CP and not due to general hand dominance or lateralization effects (289). We also noted that children with CP had lower reaching accuracy than controls, even when reaching with the preferred arm and under low time constraints. These observations are in line with the growing body of evidence detailing sensorimotor deficits in the less-impaired (preferred) arm of children with CP, with impaired domains including manual function (474), motor planning, and most pertinent to this study, visually-guided reaching and hitting performance (14, 21, 289, 463).

In contrast to our hypothesis, we observed that time constraints did not differentially affect reaching accuracy across groups, in either the preferred or the non-preferred arm. This finding could be due to the relatively lower emphasis placed on spatial accuracy compared to movement speed in the current study. Our time-constrained task emphasized movement speed (ability to move faster to reach the target within shorter time duration) over endpoint variability (ability to maintain cursor position at the target) as participants were not explicitly instructed to stop at the target location. Consequently, the movements lacked the deceleration needed to bring the arm to a fixed end-point, thus minimizing the computational burden placed on the effector system to bring the limb to a stable end-position (502). This is a key consideration as preliminary work indicates that children with CP do not adhere to the typical speed-accuracy trade-off (Fitts' law) commonly observed in healthy adults and typically developing children (503). Children with CP perform better at tasks that emphasize movement speed over end-point accuracy (504). Another factor could be that the outcome measure for reaching accuracy (dichotomous 'hit/miss' accuracy rate) for this pilot study was not sensitive enough to parse out finer between-group differences in reaching performance across time constraints. Processing of the richly detailed kinematic data provided by the KINARM robot may provide more sensitive outcomes of reaching performance (e.g., movement path variability, initial direction error) (14, 289) but these analyses were beyond the scope of this study. Finally, the imposed time constraints may not have been sufficiently challenging; however, similar declines in reaching accuracy observed at the high time constraint condition in both groups point to the adequacy of the selected time constraints in assessing reaching performance.

4.4.2. Prefrontal cortex activity

Our results indicated that children with CP exhibited lower overall PFC activity during preferred arm reaching under high time constraints, relative to both controls and reaching performed under low time constraints. A similar deactivation pattern, also specific to CP, was observed during non-preferred arm reaching under high time constraints, though this did not reach statistical significance. These novel results contradict our stated hypotheses of increased PFC

activity in children with CP under high time constraints. Surkar and colleagues reported increased PFC activity in children with hemiplegic CP relative to typically developing controls during a sequential shape-matching cognitive task performed in isolation (57, 59) and under conditions of increased postural demands (cognitive-motor dual-task) (58). One explanation for the difference in PFC activation patterns observed in our study is that our time-constrained reaching task requires greater response speed and high movement amplitudes, placing significantly greater demands on the visuo- and sensory-motor systems. Children with CP require greater neural resources to produce similar levels of motor output for both automated behaviors like walking (46, 174) and purposeful movements like goal-directed reaching. Impaired cortical processing of visuospatial (176, 177), proprioceptive (505), and sensorimotor information (180) in children with CP may also contribute to their impaired upper limb function (505). With abnormally high sensorimotor cortex activity reported in CP during simple uni-joint movements (47, 48), performing more challenging tasks like time-constrained reaching may require neural resource re-allocation (298) away from cognitive-centered prefrontal cortices toward caudal sensorimotor and multisensory association cortices in children with CP (506).

Recent work from neuroeconomics attempts to model this complex ‘constrained resource allocation’ (298). Alonso et al. (298) highlight the role of the PFC as an important node in the proposed central executive system that regulates neural resource allocation. This higher-order function of the PFC supports its critical role in mediating executive functions such as action planning, spatial attention, working memory, and error monitoring (52). In contrast to these critical functions, we observed a decrease in neural resource allocation to the PFC (deactivation) in children with CP when reaching was performed under high time constraints. Prior work in children with unilateral CP (45) and adults with stroke (507) may help explain this unexpected observation of PFC deactivation in CP. Increased sensorimotor cortical activation observed in the lesioned hemisphere of individuals with stroke during manual task performance was positively related to force production (507). Neuroimaging studies in children with CP found brain activation to be

excessive (375) and widespread (508), revealing the tendency of the damaged CNS to divert its limited neural resources to functionally important yet neurologically impaired brain areas. Notably, the magnitude of the proposed compensatory neural resource re-allocation and its impact on task performance appears co-dependent on task demands and environmental context in CP (509). Abnormally increased activity observed in the contralateral sensorimotor cortex in children with unilateral CP was related to less discrete muscle activation patterns and accompanied by inefficient movement trajectories during complex upper limb tasks like simulated pouring and asymmetric squeezing (45). Specific to the current study, similar patterns of lowered overall PFC activity were observed in children during high time constraint reaching with both the preferred and non-preferred arms. Though group differences in overall PFC activity were only statistically significant in the preferred arm, strong associations between overall PFC activity and reaching accuracy were observed in children with CP during non-preferred arm reaching under high time constraints. The lower magnitude of PFC de-activation displayed by children with CP during the latter condition may also indicate attenuated resource reallocation through greater attentional focus, mental effort or impulse control, or that other factors such as altered movement kinematics may influence PFC activation in CP. Taken together, these observations complement previous reports suggesting PFC activation is a potentially sensitive marker of task performance in children with CP (59), especially when movement challenge (135) and task demands (56) are increased, raising the possibility that PFC activation levels may serve as therapeutic targets for future interventions in this population.

4.4.3. Relationship between reaching accuracy and PFC activity

The impact of the proposed neural resource re-allocation on reaching accuracy may be reflected by the correlational analyses results. In agreement with our initial hypothesis, we observed a consistent positive relationship between PFC activity and reaching accuracy in children with CP. This observation implicates the PFC as a potentially important contributor to reaching accuracy in children with CP; the corollary is that the observed PFC *de*-activation seen in children with CP may be a pathological, counterproductive phenomenon which adversely impacts reaching performance.

The distinct PFC activity patterns observed in children with CP may serve as neurophysiological markers of functional performance. More speculatively, changes in PFC activity following intervention may accompany, precede or follow, functional gains in motor performance. Prior fNIRS work reported altered PFC activity in children with CP at the pre-intervention baseline was attenuated to levels comparable to typically developing controls following intensive upper limb therapy (59). Another study that assessed fNIRS-derived measures of cortical activity during robotic-assisted gait training reported increased PFC activity in children with moderate-to-severe spastic CP at the conclusion of 12 sessions of training (56). In both studies, the proposed 'normalization' of PFC activity was accompanied by functional improvements observed following each intervention. In contrast to the positive associations noted in CP, we observed negative trends signifying inverse relationships between overall PFC activity and reaching accuracy in controls, with a significant negative association noted only during preferred arm reaching under low time constraints. Notably, PFC activity is sensitive to task familiarization (55) and practice-based motor learning (510) in healthy adults, and could potentially indicate motor skill in neurotypical adults. Novel fNIRS work on surgical trainees revealed PFC activity patterns elicited during bimanual simulated surgeries could accurately distinguish between, and classify surgical trainees (highest PFC activity), novice surgeons (low PFC activity) and experienced surgeons (lowest PFC activity) (511), suggesting PFC activity indicates skill acquisition and learning during complex upper limb tasks in neurotypical individuals (512). These findings highlight the need for further research on task-induced PFC activation in both typically developing and neurologically impaired children, to better understand the functional relevance of the distinct PFC activation patterns observed in children with CP.

The imposition of time constraints revealed novel nuances in the reaching accuracy-PFC activity relationship in children with CP that are hemisphere-specific. Specifically, the ipsilateral PFC showed a consistent positive relationship with reaching accuracy in both arms, with stronger associations observed under low time constraints. In contrast, the contralateral PFC showed a strong

positive relationship with reaching accuracy only during non-preferred arm reaching performed under high time constraints. These results are in line with those of an exploratory pilot fNIRS study that observed PFC activity was lateralized to the ipsilateral PFC in two adults with CP during a ball throwing motor task compared to bilateral dominance seen in the healthy adult controls (352). While no statistical conclusions could be drawn, the authors speculated that the PFC's functional response to a visuomotor upper limb task may differ in CP compared to healthy individuals. Our novel observations provide support to this exploratory hypothesis and shed light on a previously unexplored aspect of the cortical regulation of reaching in CP. In summary, these findings illustrate the complexity of the cognitive-visual-sensorimotor system interaction that underlies successful goal-directed reaching in children with CP.

The novel observations reported above are supported by several strengths in our study design. Our study sample, while modest in size, was tightly controlled, with only right-arm dominant participants in both the age- and sex-matched groups that did not differ in any commonly measured physical characteristics. We attempted to minimize the heterogeneity of the CP group by restricting enrollment to participants who were within a reasonably narrow age range (5-11 y), exhibited clinically detectable spasticity, were independent ambulators (GMFCS levels I and II), and had mild impairments in manual abilities (MACS levels I and II). Motions artifacts commonly reported in work using fNIRS with neurological populations (513) were minimized during data collection by stabilizing the head within the KINARM frame and by using a chinrest, with additional automated motion artefact correction performed during data processing. Our reaching task was methodologically rigorous, with target location spatially randomized in a uniform distribution in both the x- and y- direction to minimize task predictability and increase trial-by-trial variability to prevent the decline in PFC activity observed across similar trials (55).

This work also has limitations. First, fNIRS technology is limited to the collection and interpretation of neurophysiological data from the outermost layer of the cerebral cortex; thus, we could not image sub-cortical regions like the inter-connected basal nuclei and cerebellar networks

that also play an important role in movement planning and coordination (514). The low spatial resolution of the fNIRS device we used (Portalite, Artinis) also precluded imaging of other areas within the PFC and other cortical regions of interest like the sensorimotor and parietal cortices. While restricted in its spatial resolution, the Portalite device has previously been used to assess PFC hemodynamics in school-aged children (496, 515). Second, the Portalite device also lacks the integration of short-separation channels that could account for hemodynamic changes arising from systemic physiology (blood pressure, respiration and heart rate changes, etc.). Though we cannot exclude the possibility of fNIRS signal contamination from these variables, recommendations for best practices in fNIRS processing were followed to minimize these contaminants (402). Third, the modest sample size did not allow us to conduct further sub-group analyses (e.g., unilateral versus bilateral CP) and restricts the generalizability of our results. Despite this limitation, statistically significant group differences in reaching accuracy and PFC activity were noted, with significant positive relationships between reaching accuracy and PFC activity also detected in the children with CP. Finally, we did not collect data on eye movements, perceptual impairments, or proprioception that could shed further light on the underlying bases of the observed accuracy deficits during reaching in children with CP. However, previous work examining the relationship of proprioception and robotic reaching performance in children with hemiplegic CP showed a surprising dissociation of proprioceptive impairments from reaching performance, highlighting that perinatal stroke may differentially affect the sensory and motor systems (17). We recognize that more detailed kinematic analyses could provide greater insights into the limb- and time constraint-specific deficits observed in children with CP, with the slower, jerkier, more variable and less accurate reaching movements displayed by children with spastic CP (289, 457, 516) all potentially contributing to the observed accuracy deficits reported in this study. Detailed multivariate analyses of reaching kinematics (517) should be the focus of future studies to assess the role of specific kinematic parameters such as movement trajectory characteristics and velocity profiles on reaching performance across time constraints in children with CP.

4.5. Conclusions

Our study is the first to reveal distinct PFC activity patterns in children with spastic CP during robotic time-constrained reaching. Specifically, contrasting patterns of PFC activity were noted across time constraints in children with CP (PFC deactivation) compared to age-, sex- and arm dominance-matched typically developing controls (PFC activation). Correlation analyses revealed moderate-to-strong relationships between PFC activity and reaching accuracy across time constraints, with PFC activation patterns indicating possibly distinct roles of each hemisphere during time-constrained reaching in children with CP. Our results support the feasibility of using fNIRS in conjunction with robotic technologies to simultaneously assess the cortical correlates and performance metrics of goal-directed upper limb movements in children with CP.

CHAPTER 5

REACHING KINEMATICS AND THEIR RELATIONSHIP WITH PREFRONTAL CORTEX ACTIVITY PATTERNS DURING MOVING TARGET INTERCEPTION IN CHILDREN WITH CEREBRAL PALSY

[1]Khan, O.A., Rahman, S., Singh, T. Barany, D., Pottumuthu, S., Modlesky, C.M. 2025. *To be submitted to a peer-reviewed journal*.

Abstract

Introduction: Suppressed prefrontal cortex (PFC) activity in children with cerebral palsy (CP) is linked to reduced accuracy when reaching for stationary targets, but the impact of PFC activity on moving target interception is unknown. This study aimed to concurrently assess motor performance and PFC activity during time-constrained interception of moving targets in children with CP. We hypothesized interception performance deficits observed in CP would be directly related to their PFC activity.

Method: Fifteen children with spastic CP (5-11y; Manual Ability Classification System level I-II) and 15 age-, sex-, and race-matched typically developing control children performed rapid unimanual reaching with a robotic manipulandum (KINARM) to intercept horizontally moving targets projected onscreen. Task difficulty was modulated by varying target velocity (high vs low time constraints). Ten trials per block, and 4 blocks per arm were completed. Mobile functional near-infrared spectroscopy was used to assess PFC activity.

Results: Children with CP exhibited impaired motor performance (lower accuracy, d = 0.846; greater spatial errors, d = 0.929) and planning deficits (slower reaction time, d = 0.993), alongside more suppressed contralateral PFC activity (d = 0.522) and altered PFC laterality (ipsilateral dominance in CP vs. contralateral dominance in controls, d = 1.073) compared to controls during non-preferred arm interception (all $p < 0.05$). Performance deficits were exaggerated under more challenging high time constraints, with the CP cohort demonstrating higher spatial errors (d = 1.233) and lower reaching peak velocities (d = 0.756) than controls (both $p < 0.05$). Under low time constraints, relationships of contralateral PFC dominance with reaction time demonstrated opposing patterns in children with CP and controls (Spearman rho (r_s) = 0.516 and -0.546, respectively; both $p < 0.05$). Conversely, greater contralateral PFC activity and dominance in controls during preferred arm interception were related to poor motor performance under high time constraints (r_s range = -0.590 to 0.823, all $p < 0.05$).

Conclusion: Impaired motor performance and atypical PFC activity, coupled with contrasting arm- and group-specific patterns of PFC-performance associations highlight disrupted brain-behavior relationships fin children with CP. Tailored rehabilitation strategies targeting aberrant PFC activity patterns may improve arm function in this group.

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5.1. Introduction

Cerebral palsy (CP) describes a diverse group of neurodevelopmental disorders of posture and movement arising from a non-progressive brain injury (2). Up to 60% of children with CP experience upper limb impairments that limit functional independence in self-care, daily activities, and recreation (6, 113, 136). Beyond sensorimotor deficits such as weakness (476), dyscoordination (283, 518), and poor postural control (519, 520), individuals with CP experience challenges in movement planning (8), visuomotor coordination (521), and visuospatial attention-perception (112, 522) that impede successful goal-directed actions. The interception of moving targets is an essential component of many real-world activities such as catching, hitting, and interacting with moving items, and is especially susceptible to this complex interplay of multisystemic deficits. Interception demands the seamless integration of sensory-perceptual, attentional, and motor processes to detect, track, and predict object movement in dynamic environments while concurrently planning and executing precisely coordinated and timed limb movements toward an object's anticipated position (27-29). This real-time coupling of feedback-driven corrections with anticipatory feedforward adjustments (30) also makes interception tasks uniquely suited to probe aberrant goal-directed behaviors in those with brain injury. In individuals with CP, sensory processing deficits produce aberrant somatosensory feedback (32) and prolonged response latencies which, coupled with spatial inattention (9) and perceptual deficiencies (490), may increase their dependence on feedforward-based predictive motor strategies (30). These impairments are compounded by central deficits in upper limb action planning which resist resolution over the course of development (34) and restrict arm use (35, 36). However, current clinical assessments of arm and hand use are unidimensional and lack the sensitivity and objectivity to accurately and reliably detect subtle deficits (11), underscoring the need for holistic and ecologically valid assessment tools to better characterize upper limb dysfunction in CP.

Robotic technologies enable sensitive, reliable, and multidimensional assessment of reaching performance and planning in children with CP, with high-resolution kinematic metrics

capturing subtle deficits in sensorimotor (13, 14, 17, 20), visuospatial (21), and executive functions (22) that are often undetected on standardized clinical tests. When combined with neurophysiological evaluations (15, 16) and functional neuroimaging (167, 305, 464), robotic assessments can provide mechanistic insight into brain-behavior relationships across a range of task contexts. Functional near-infrared spectroscopy (fNIRS) is a non-invasive, mobile functional neuroimaging modality that is easily integrated with robotic platforms, and complements robotic assessments by providing real-time mapping of cortical activation patterns during naturalistic behaviors such as walking (56), stepping (135) and reaching (55, 495). Recent evidence (188) supports the feasibility of fNIRS in CP, with the prefrontal cortex (PFC) emerging as a key cortical region of interest (56-59, 135, 352) due to its high accessibility, superficial location, and critical role in coordinating cognitive-motor interactions. Studies using fNIRS in CP reported task-dependent PFC activity patterns during motor actions, reflecting its complex role in mediating action planning (523), prediction (52), executive functioning (293), and decision-making processes (53) that are integral to successful goal-directed reaching. These functions are particularly important under conditions of high task complexity or time constraints, where PFC-driven regulation of spatial attention (494), gaze-orientation (51), and goal specification (291) is integral to behavioral outcomes.

We previously combined fNIRS assessment of PFC activity with robotic evaluation of time-constrained reaching in children with CP (464), and observed suppressed PFC activity in those with CP compared to tightly matched typically developing control children. However, higher PFC activity was linked to better reaching accuracy only in CP (464), suggesting PFC activity reflects increased cognitive engagement as a possible compensatory mechanism for motor performance deficits. These novel observations underscore the value of a multimodal robotic-functional neuroimaging approach to probe adaptive cortical recruitment and compensatory behavioral strategies during goal-directed movements in CP. Though interceptive behaviors place significant demands on predictive control and action planning functions known to be mediated by the PFC, to

our knowledge, no studies have integrated robotic and portable neuroimaging tools to interrogate PFC activity during time-constrained interception. This study extended our multimodal fNIRS-robotics investigational approach (464), and aimed to concurrently assess PFC activity, reaching kinematics, and interception performance in children with CP during a time-constrained, moving-target interception task. Given their expected deficits in PFC-mediated functions like spatial attention and motor planning, and our prior observation of group-level suppression of PFC activity in CP, we hypothesized that children with CP would exhibit greater interception performance deficits, and lower and more lateralized PFC activity than typically developing children. Additionally, we anticipated greater PFC activity would be related to better motor preparedness, planning, and interception performance in children with CP.

5.2. Methods

5.2.1. Participant recruitment

Recruitment of children with spastic CP (age 5-11 y) was done for a larger randomized controlled trial (NCT03484078; clinicaltrials.gov/ct2/show/NCT03484078) via outreach to schools, rehabilitation clinics, Children's Healthcare of Atlanta, and the Cerebral Palsy Foundation between March 2019 and March 2024. Typically developing children matched to the CP group by age (± 1.5 y), sex, and race were similarly recruited as controls if they had no neurological diagnoses, height and body mass between the 5th and 95th percentiles for their age and sex, and not participating in high-level sports. Exclusion criteria included: [1] Manual Ability Classification System (MACS) level V, indicating severe limitations in handling objects and performing simple tasks, [2] cognitive impairments preventing understanding of basic verbal instructions, [3] botulinum toxin injections within six months of enrollment, or [4] significant visual or musculoskeletal impairments that would hinder testing. Ethical approval was obtained from the Institutional Review Board at the University of Georgia. Parental informed consent and participant assent were obtained before study initiation.

5.2.2. Anthropometrics and clinical assessments

Height was measured using a stadiometer (Seca 217; Seca GmbH & Co. KG., Germany) and body mass was measured using a digital scale (Detecto 6550, Cardinal Scale, MO, USA). Age- and sex-based percentiles for body mass, height, and body mass index (BMI) were calculated using US population-based normative data (467). Hand preference was determined with the Edinburgh Handedness Inventory-Short Form (468). Muscle tone was assessed using the Hypertonia Assessment Tool (HAT) (470). Manual ability and gross motor function was classified using the MACS (221) and the Gross Motor Function Classification System (GMFCS) (469), respectively.

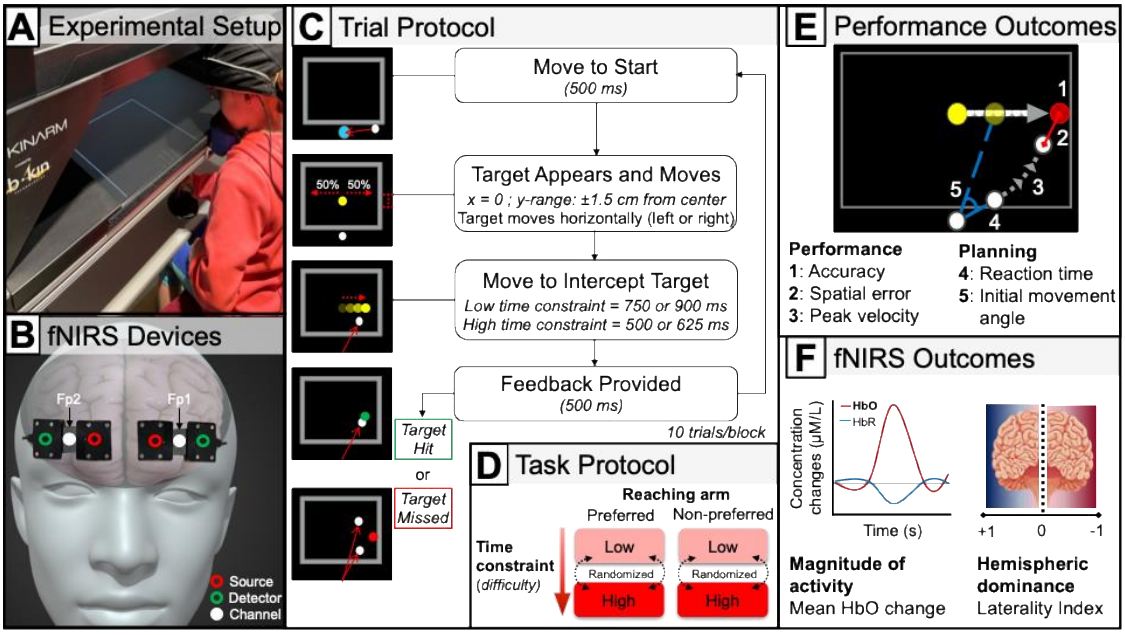

Figure 5.1. Study methods. (**A**) Experimental setup illustrating participant's seated position and unimanual grasp of the KINARM robotic handle. (**B**) Dual functional near-infrared spectroscopy devices were secured over prefrontal cortex regions of interest based on the International 10/20 system (Fp1, Fp2). (**C**) Trial protocol and (**D**) task protocol for the moving target interception task. (**E**) Interception performance outcomes were categorized into motor performance and motor planning metrics. (F) Neural (fNIRS) outcomes included measures of PFC activity magnitude and hemispheric dominance. *HbO* oxyhemoglobin, *HbR* deoxyhemoglobin.

5.2.3. Experimental setup

The experimental setup (**Fig. 5.1A**) and fNIRS device placement (**Fig. 5.1B**) have previously been detailed (266, 464). Briefly, seated participants stabilized their head on a chinrest and viewed stimuli projected onto a semi-transparent mirror. Participants grasped and moved a robotic manipulandum (KINARM End-Point, Ontario, Canada) in the horizontal plane to control an on-screen cursor, with the screen blocking visual feedback of arm movements. The experimental workspace (34 x 34 cm grey box; **Fig. 5.1C**) required participants to initiate trials by maintaining the cursor (1 cm diameter white circle) in the start position (2 cm diameter blue circle) for 500 ms. The target (1 cm diameter yellow circle) then appeared at the midline (x = 0, y-position ± 0.5 cm from center) and moved horizontally to the left or right (equal probability) at a fixed velocity. Task difficulty was modulated by imposing time constraints through varying target velocity across blocks: low time constraint blocks were easier and featured slow moving targets visible for 750 ms or 900 ms, while high time constraint blocks were harder with rapidly moving targets visible for 500 ms or 625 ms. Participants were instructed to intercepts targets as quickly and accurately as possible without needing to stop at the target position; successful hits (i.e., cursor-target overlap within time constraint) turned the target green, while misses resulted in the target turning red on contact with the workspace boundary. Trial feedback (500 ms) was followed by a 2000 ms interval before the next trial. Rest periods (25-30 s) where participants remained still, were included before and after each block to allow PFC hemodynamics to return to baseline. Participants performed four blocks of 10 trials each per arm, with block order randomized within each arm (**Fig. 5.1D**).

5.2.4. Data processing: (A) KINARM processing

KINARM data were sampled at 1000 Hz, exported to MATLAB (v. R2015a SP1; MathWorks, Natick, MA), and processed in Python (v. 3.10). Raw hand position and velocity data were smoothened using a low-pass, fourth-order Butterworth filter (5 Hz cut-off). **Figure 5.1E** illustrates interception outcomes. Interception **accuracy** was computed as the percentage of hits

per block. **Spatial error** was quantified as the Euclidean distance between cursor and target positions at movement offset. As participants were not required to stop at the target, movement offset was defined as the first instance of cursor-target overlap, or when the cursor crossed the y-position of the target. **Peak velocity** was assessed as the highest tangential velocity achieved during each trial. Movement onset was defined as the time when hand velocity first exceeded 5% of the initial local peak, with **reaction time** calculated as the interval between target appearance and movement onset. Trials with unidentified movement onsets or improbable reaction times (<100 ms or exceeding trial duration) were excluded. **Initial movement angle**, measured at 50 ms post-reaction time, was computed as the angular deviation between start-to-hand and start-to-target position vectors. Positive angles indicated leading trajectories aimed ahead of the current target position, while negative angles reflected lagging trajectories directed towards the current target position.

5.2.4. Data processing: (B) Functional neuroimaging (fNIRS) setup and processing

Two portable fNIRS devices (Portalite, Artinis Medical Systems, The Netherlands) were positioned on the participants' forehead (Fp1 and Fp2 locations of the International 10-20 system) over the left and right PFC, respectively (**Fig. 5.1B**), and secured with black felt caps to minimize signal contamination. Data from the 3 cm channel (135, 464, 496), sampled at 50 Hz, were processed using the HOMER3 software (v1.28.1) in MATLAB (MathWorks, Natick, MA, USA) following best practices (402). Preprocessing included power spectral density checks for signal quality, conversion of light intensity to optical density changes, and band-pass filtering (cut-offs = 0.01-0.08 Hz) to remove cardiorespiratory noise, Mayer waves, and slow drifts (362). Motion artifacts and resultant baseline shifts were corrected using a hybrid spline interpolation-Savitzky Golay method (441). A principal component analyses filter accounted for systemic physiological contamination by removing 80% of spatially covarying signal components across fNIRS channels (524, 525). Hemoglobin concentration changes were computed (partial pathlength factor = 1) (135), baseline corrected by subtracting the mean signal from the preceding 2 seconds of each block, and

block averaged. **Figure 5.1F** depicts fNIRS outcomes. Mean changes in oxyhemoglobin concentration over 45 seconds post-trial onset indicated magnitude of PFC activity (464). A laterality index (LI, **Equation 5.1**) was used to quantify PFC lateralization, categorizing hemispheres as ipsilateral or contralateral to the arm tested (526). Positive LI values indicated contralateral PFC dominance, negative values reflected ipsilateral PFC dominance, and values near zero suggested bilateral dominance.

$$Laterality\ index\ (LI) = \frac{\partial HbO_{Contralateral} - \partial HbO_{Ipsilateral}}{\partial HbO_{Contralateral} + \partial HbO_{Ipsilateral}} \qquad \textit{(Equation 5.1)}$$

5.2.5. Statistical analysis

Statistical analyses were conducted in RStudio (v2022.07.2, R Core Team 2022). Normality of data was assessed in SPSS (v27.0.1, IBM Corp., Armonk, NY) using skewness, kurtosis, and the Shapiro-Wilk test. Independent t-tests or non-parametric Mann-Whitney *U* tests were used to evaluate group differences in physical characteristics, based on normality. One-sample t-tests were used to assess deviations of physical characteristic percentiles from age- and sex-based 50th percentiles. Linear mixed-effect models in RStudio were used to analyze interception performance outcomes (accuracy, spatial error, reaction time, initial angle, peak velocity) and PFC activity (oxyhemoglobin concentration change, Laterality Index), to account for the nested data structure of fNIRS datasets (437). Fixed effects included group (CP versus controls), arm (preferred versus non-preferred), and time constraint [high (hard) versus low time constraint (easy)], with subject as a random effect to account for correlations arising from repeated measures. Significant effects were followed by pairwise comparisons (alpha = 0.05). Spearman rank correlation (r_s) was used to assess relationships between PFC activity and interception performance. Effect sizes (Cohen's d (*d*)) were categorized as small (0.2), medium (0.5), or large (0.8) (473).

5.3. Results

5.3.1. Participant characteristics

Fifteen children with spastic CP and 15 age-, sex- and race-matched typically developing control children met participation criteria (**Table 5.1)**. Groups did not differ in any height, body mass, or BMI (all $p > 0.05$), and percentiles did not differ from age- and sex-based 50th percentiles in either group (all $p > 0.05$).

Table 5.1. Physical characteristics of children with cerebral palsy (CP) and typically developing control children (Con).

	CP (n = 15)	Con (n = 15)	*d*	*p*
Age (y)	8.4 ± 1.8	8.4 ± 2.1	0.017	0.962
Sex (male/female)	7/8	7/8	—	—
Race (White/Black)	13/2	13/2	—	—
Height (m)	1.3 ± 0.1	1.3 ± 0.1	0.120	0.744
Height %	50 ± 36	61 ± 25	0.371	0.443
Body mass (kg)	29.5 ± 10.0	29.8 ± 10.9	0.029	0.983
Body mass %	50 ± 31	56 ± 28	0.217	0.558
BMI	17.0 ± 2.8	16.7 ± 2.7	0.126	0.885
BMI %	54 ± 28	53 ± 26	0.026	0.944
Arm dominance (right/left)	6/9	14/1	—	—
CP diagnosis (unilateral/bilateral)	8/7	—	—	—
MACS level (I/II)	3/12	—	—	—
GMFCS level (I/II)	11/4	—	—	—
HAT preferred arm	11[a]/1[b]/1[c]/2[d]	15[a]/0[b]/0[c]/0[d]	—	—
HAT non-preferred arm	8[a]/4[b]/0[c]/3[d]	15[a]/0[b]/0[c]/0[d]	—	—

All values are mean ± SD. % represents percentiles for height, body mass, and BMI. Percentiles did not differ from age- and sex-based 50th percentiles. [a]Normal tone, [b]spasticity, [c]dystonia, [d]mixed tone (spasticity with dystonia).

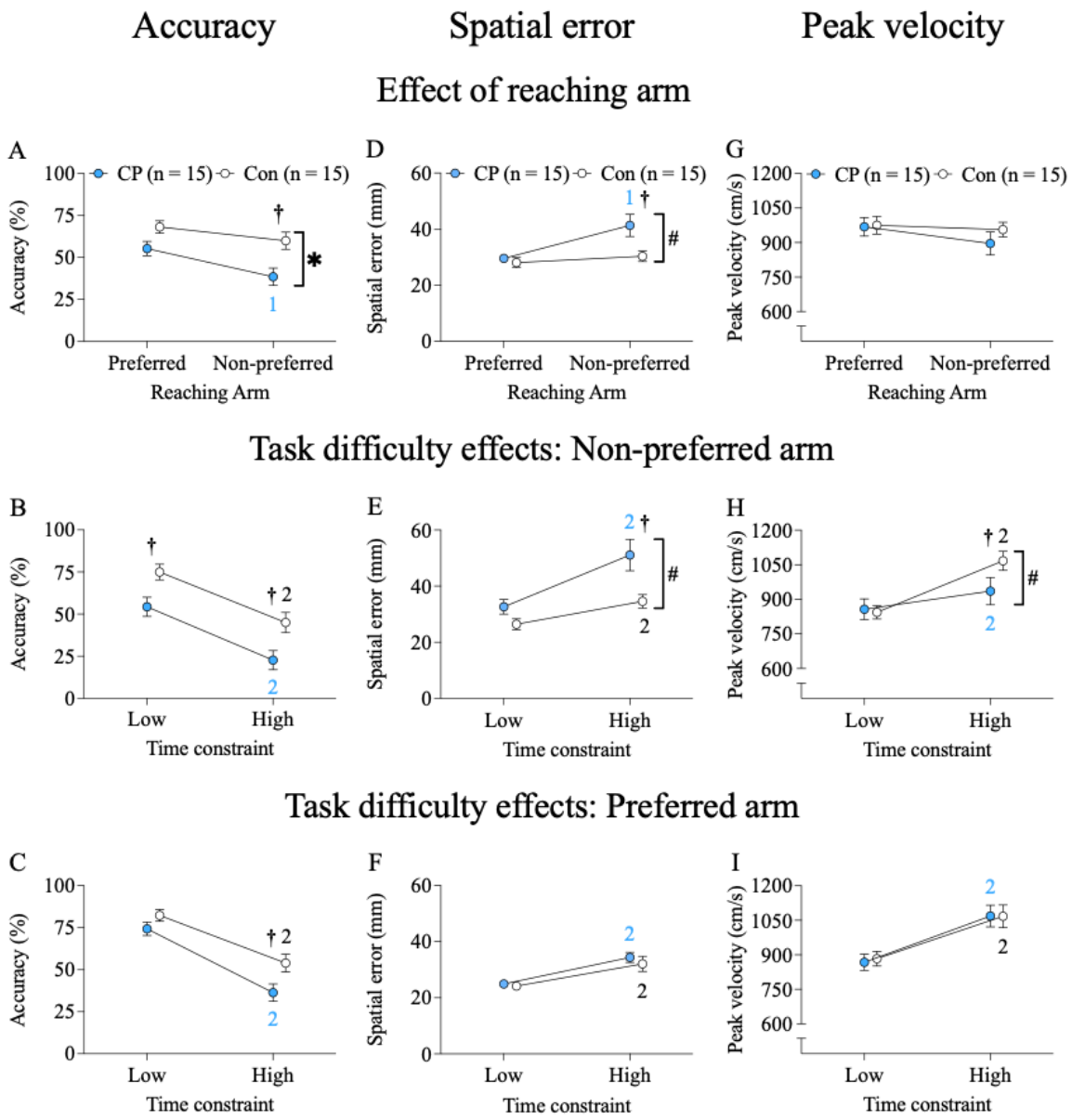

Figure 5.2. **Motor performance (accuracy, spatial error, peak velocity) for time-constrained interception**. Results are presented for each arm (A, D, G), and across levels of task difficulty (low, high time constraint) for the non-preferred arm (B, E, H) and the preferred arm (C, F, I). All values are mean ± SE. # Group-by-arm or group-by-time constraint interaction, ✱group effect, †group difference, [1]arm difference (CP, Con), [2]time constraint difference (CP, Con). CP, cerebral palsy; Con, typically developing control children.

5.3.2. Interception outcomes: Motor performance

The effect of group, reaching arm, and time constraint on interception performance (i.e., accuracy, spatial error, and peak velocity) is illustrated in **Figure 5.2**. A group effect for **accuracy** revealed lower accuracy in children with CP than controls (d = 0.675, p = 0.009; **Fig.**

5.2A), with group differences detected in the non-preferred arm (d = 0.846, p = 0.005) but not the preferred arm (d = 0.505, p = 0.086). Children with CP displayed lower accuracy with the non-preferred arm than the preferred arm (d = 0.663, p = 0.004), while accuracy rates in controls did not differ between arms (d = 0.321, p = 0.153). Those with CP displayed lower accuracy than controls across low and high time constraints in the non-preferred arm (d = 0.964 and 1.042, respectively; both $p < 0.05$; **Fig. 5.2B**), but only at the more difficult high time constraint condition in the preferred arm (d = 1.003, p = 0.009; **Fig. 5.2C**).

A group-by-arm interaction for **spatial error** (p = 0.009, **Fig. 5.2D**) revealed greater spatial errors in children with CP during non-preferred arm interception compared to controls (d = 0.929, p = 0.003), and to their preferred arm (d = 0.998, $p < 0.001$). With the non-preferred arm, children with CP exhibited higher spatial errors under high time constraints compared to controls (d = 1.233, p = 0.002; **Fig. 5.2E**), with both groups demonstrating higher spatial errors in this challenging condition compared to the easier low time constraint condition (d_{CP} = 1.379, d_{Con} = 0.607; both $p < 0.05$; **Fig. 5.2E**).

Peak velocity did not differ between groups in either arm, or across arms in either group (d range = 0.039 - 0.378, all $p > 0.05$; **Fig. 5.2G**), though a trend for slower movements with the non-preferred compared to the preferred arm was noted in children with CP (d = 0.378, p = 0.052). Children with CP exhibited lower peak velocities than controls specifically under high time constraints in the non-preferred arm (d = 0.756, p = 0.046; **Fig. 5.2H**). Both groups demonstrated greater peak velocity under high compared to low time constraints in the non-preferred arm, though the magnitude of differences was markedly reduced in those with CP (d_{CP} = 0.452, d_{Con} = 1.284; **Fig. 5.2H**).

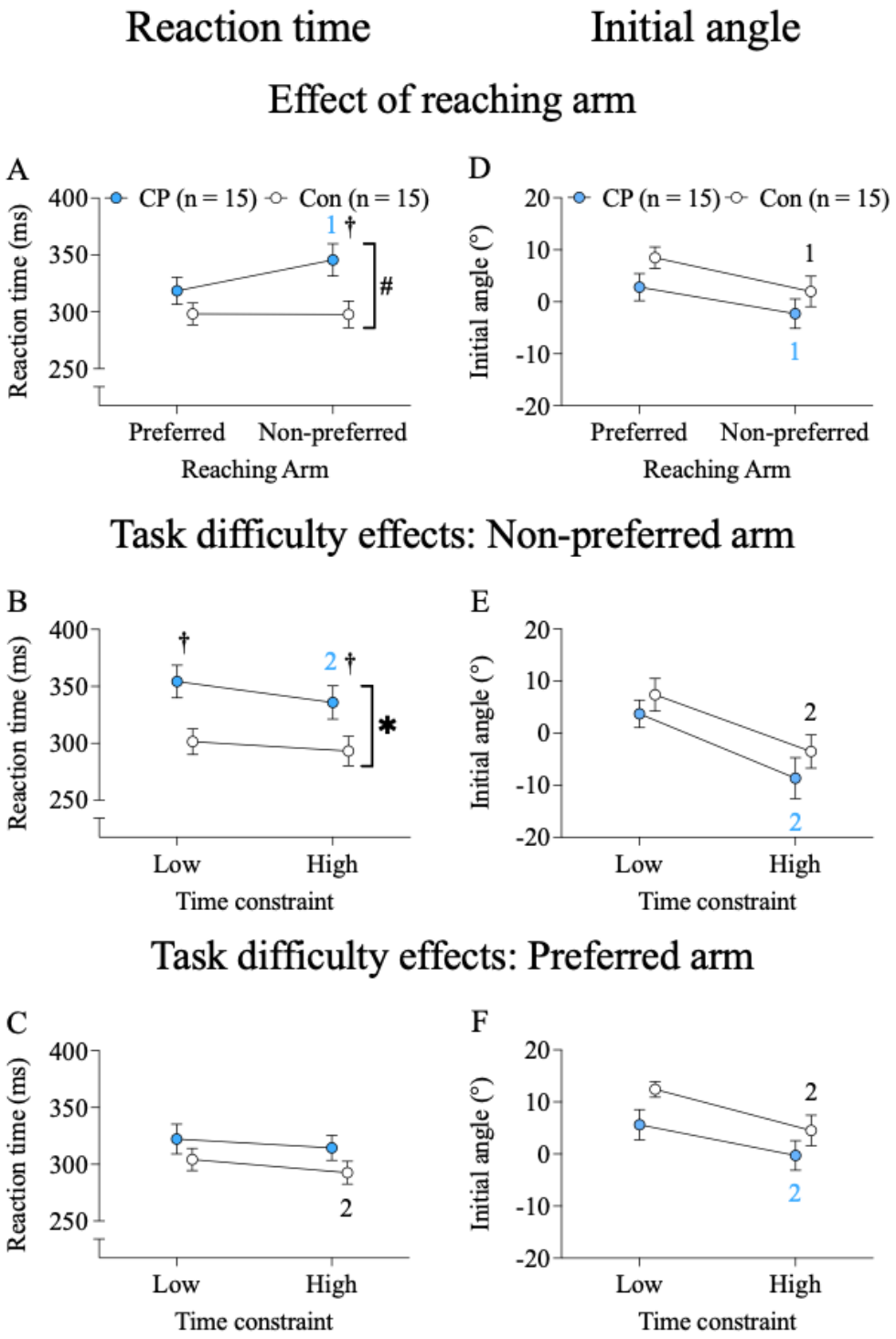

Figure 5.3. **Motor preparedness (reaction time) and planning (initial movement angle) for time-constrained interception**. Results are presented for each arm (A, D), and across levels of task difficulty (low, high time constraint) for the non-preferred arm (B, E) and the preferred arm (C, F). Positive values of initial movement angle indicate reaching trajectory directed ahead of (i.e., leading) the target position, while negative values indicate reaching trajectory directed behind (i.e., lagging or following) the target position. All values are mean ± SE. #Group-by-arm interaction, ✱group effect, †group difference, [1]arm difference (CP, Con), [2]time constraint difference (CP, Con). CP, cerebral palsy; Con, typically developing control children.

5.3.3. Interception outcomes: Motor planning

The effect of group, reaching arm, and task difficulty (time constraint) on interception planning metrics is illustrated in **Figure 5.3**. A group-by-arm interaction for **reaction time** ($p < 0.001$, **Fig. 5.3A**) revealed slower reaction time in CP during non-preferred arm interception compared to controls ($d = 0.993$, $p = 0.008$) and to their preferred arm ($d = 0.557$, $p < 0.001$). Children with CP displayed slower reaction times than controls across low and high time constraints with the non-preferred arm ($d = 1.016$ and 0.819, respectively; both $p < 0.05$; **Fig. 5.3B**). Faster reaction time during the high compared to the low time constraint condition was observed with the non-preferred arm in those with CP ($d = 0.354$, $p = 0.009$; **Fig. 5.3B**), and with the preferred arm in controls ($d = 0.269$, $p = 0.020$; **Fig. 5.3C**).

An arm effect was observed for **initial movement angles** ($p = 0.001$, **Fig. 5.3D**), which lower in the non-preferred arm than the preferred arm ($d = 0.472$, $p = 0.001$). Both groups displayed lower initial angles during high compared to low time constraints in the non-preferred ($d_{CP} = 0.976$, $d_{Con} = 0.859$, both $p < 0.05$; **Fig. 5.3E**) and preferred arm ($d_{CP} = 0.582$, $d_{Con} = 0.776$, both $p < 0.05$; **Fig. 5.3F).**

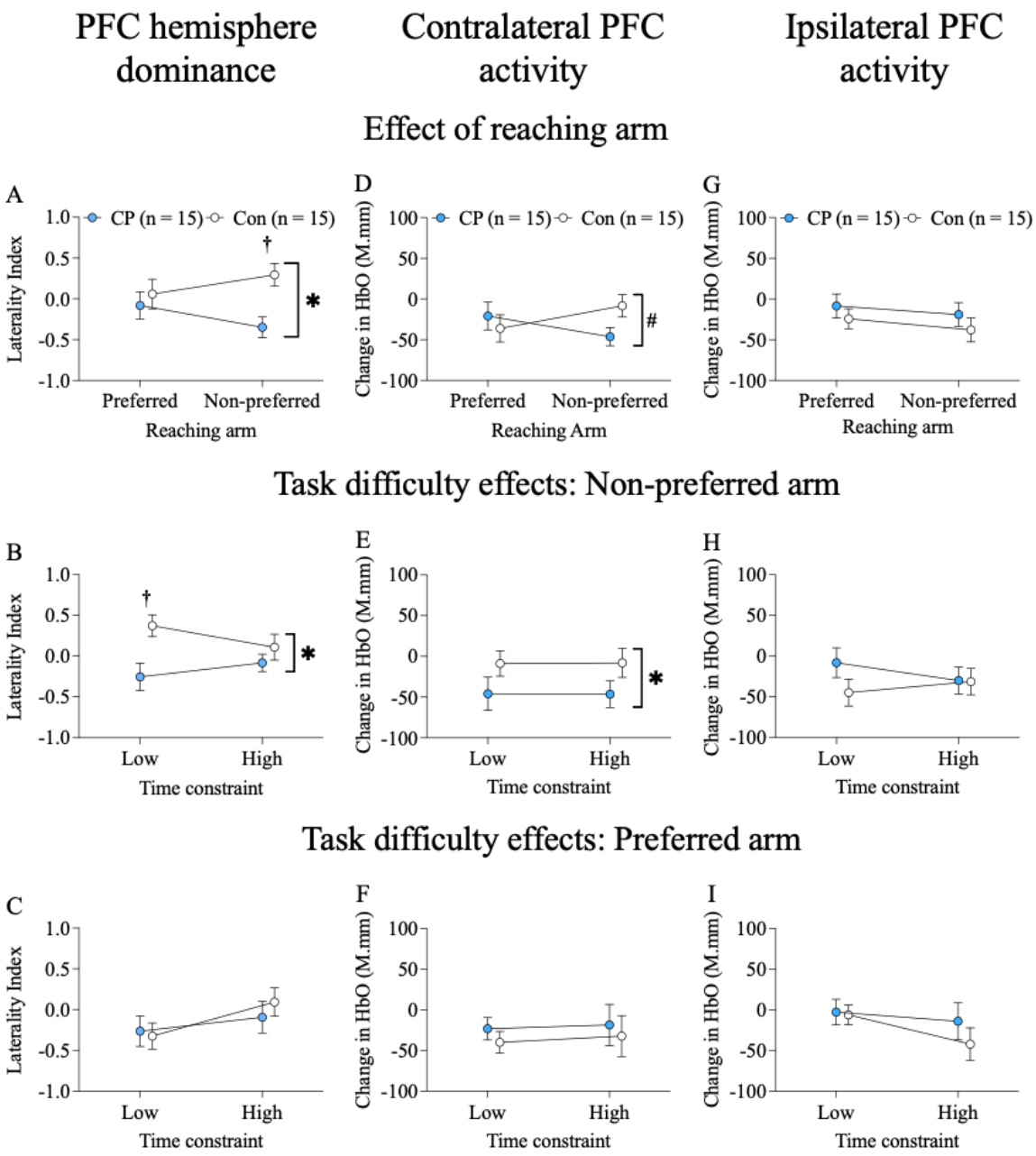

Figure 5.4: Task-evoked PFC activity (contralateral PFC, ipsilateral PFC) and hemispheric dominance (laterality index) for time-constrained interception. Results are presented for each arm (A, D, G), and across levels of task difficulty (low, high time constraint) for the non-preferred arm (B, E, H) and the preferred arm (C, F, I). Positive values of laterality index indicate contralateral PFC dominance, while negative values indicate ipsilateral PFC dominance. All values are mean ± SE; # Group-by-arm interaction, ✱group effect, †group difference. CP, cerebral palsy; Con, typically developing control children.

5.3.4. fNIRS outcomes: Prefrontal cortex activity

The effect of group, reaching arm, and time constraint on PFC activity magnitude and laterality is illustrated in **Figure 5.4.** A group effect for **PFC lateralization** revealed overall lower

LI in children with CP compared to controls (d = 0.644, p = 0.019; **Fig. 5.4A**), with differences restricted to the non-preferred arm (d = 1.073, p = 0.005). Group differences in this arm were observed only during low time constraint conditions, with children with CP displaying ipsilateral PFC dominance compared to contralateral dominance in controls (d = 1.126, p = 0.003; **Fig. 5.4B**). A group-by-arm interaction for **contralateral PFC activity** (p = 0.041, **Fig. 5.4D**) revealed a trend for lower activity in CP compared to controls in the non-preferred arm (d = 0.522, p = 0.054), with similar trends observed under both time constraints (**Fig. 5.4E**). There was no effect of group, arm, or time constraint on **ipsilateral PFC activity** (all p > 0.05, **Fig. 5.4G-I**).

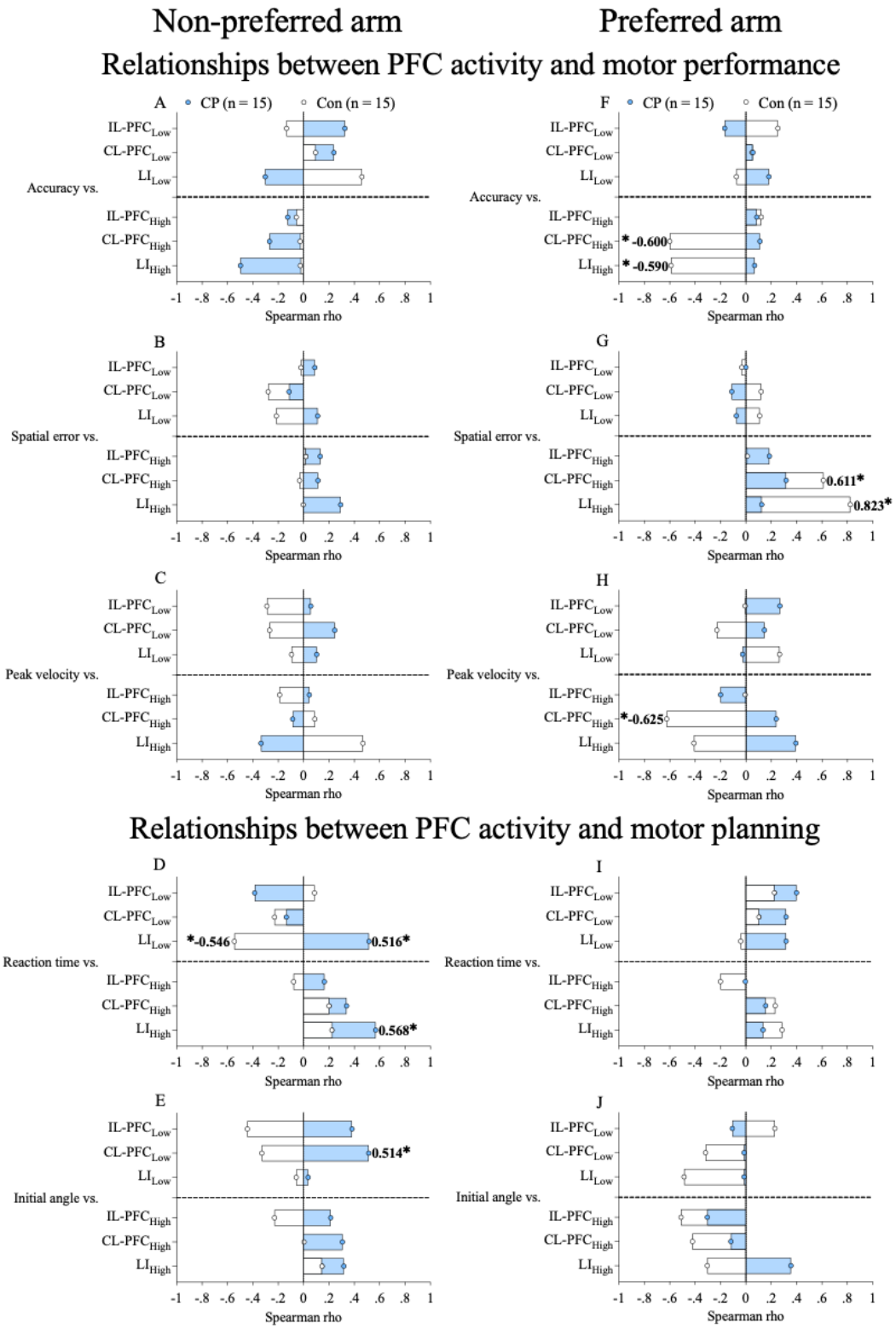

Figure 5.5: Spearman correlational analyses. Relationships of PFC activity magnitude (Contralateral, CL-PFC; Ipsilateral, IL-PFC) and hemispheric dominance (Laterality Index, LI) with interception performance [accuracy (A,F), spatial error (B,G), peak velocity (C, H)] and planning [reaction time (D,I), initial movement angle (E,J)] across time constraints (low, high) with the non-preferred (A-E) and preferred arm (F-J) in children with CP and typically developing children (Con). *Statistically significant relationships.

5.3.5. Relationship between prefrontal cortex activity and motor performance

In the preferred arm, PFC activity was not related to interception performance in CP (all $p > 0.05$; **Fig. 5.5F-H**); however, greater contralateral PFC activity was linked to worse interception performance in controls. Significant relationships were observed specifically under high time constraints, with greater contralateral PFC activity in controls related to lower accuracy ($r_s = -0.600$, $p = 0.018$; **Fig. 5.5F**), higher spatial error ($r_s = 0.611$, $p = 0.016$; **Fig. 5.5G**) and lower peak velocity ($r_s = -0.625$, $p = 0.013$; **Fig. 5.5H**). Similarly, greater contralateral PFC dominance in controls was also linked to poor performance outcomes under high time constraints, with higher LI values related to worse accuracy ($r_s = -0.590$, $p = 0.021$; **Fig. 5.5F**) and greater spatial error ($r_s = 0.823$, $p < 0.001$; **Fig. 5.5G**). No significant relationships between PFC activity and performance were observed with the non-preferred arm in either group (all $p > 0.05$).

5.3.6. Relationship between prefrontal cortex activity and motor planning

In the non-preferred arm, significant associations between PFC activity and motor planning were observed for both groups (**Fig. 5.5D-E**). Specifically, higher LI values (i.e, stronger contralateral PFC dominance) in children with CP was related to slower reaction time across low and high time constraints ($r_s = 0.516$ and 0.568, respectively; both $p < 0.05$; **Fig. 5.5D**). Conversely, in controls, higher LI values were related to faster reaction time under low time constraints ($r_s = -0.546$, $p = 0.035$; **Fig. 5.5D**). Greater contralateral PFC activity in those with CP was also related to higher initial movement angles under low time constraints ($r_s = 0.514$, $p = 0.050$; **Fig. 5.5E**).

5.4. Discussion

This novel multimodal study combined robotic assessment of time-constrained moving-target interception with mobile functional neuroimaging to investigate motor performance, planning, and PFC activity in children with CP compared to age-, sex-, and race-matched typically

developing control children. Children with CP exhibited impaired performance and planning with the non-preferred arm, evidenced by reduced accuracy and increased spatial errors, alongside prolonged reaction times compared to controls. Group differences were amplified under more difficult high time constraints, with lower peak velocity in those with CP indicating challenges in adapting behavior to meet heightened task demands. Cortical activity patterns during non-preferred arm interception also differed between groups, with ipsilateral PFC dominance observed in children with CP compared to contralateral PFC dominance noted in controls. These contrasting patterns were differently linked to motor planning in each group under low time constraints, with greater contralateral dominance related to slower reaction time in CP, but faster reaction times in controls. Further, greater contralateral PFC activity in controls during preferred arm interception was also related to worse motor performance, highlighting distinct brain-behavior dynamics underlying motor performance in each group.

5.4.1. Interception performance and planning

The performance deficits observed in our cohort of children with CP align with prior literature documenting impaired interceptive behaviors in this group. While children with unilateral CP display preserved motor adaptability under external time constraints during walk-and-intercept tasks (282, 284), interception success is lower with the more impaired arm during these gait-based tasks (285), reflecting the neuromotor challenge of coordinating whole-body movements with precisely timed reaching. Similar limitations emerge during seated interception (289), with greater spatial errors, lower accuracy, longer reaction and movement times, and lower peak velocities reported in children with unilateral CP with the non-preferred arm. Notably, limb differences in mean spatial errors were 3 times greater in the CP cohort compared to typically developing children (289). Our observations corroborate and expands on these patterns by detailing markedly greater limb differences in overall spatial errors (d_{CP} = 0.998, d_{Con} = 0.194), accuracy (d_{CP} = 0.663, d_{Con} = 0.321), reaction time (d_{CP} = 0.557 , d_{Con} = 0.022) and peak velocity (d_{CP} = 0.378, d_{Con} = 0.106) in a more clinically diverse group of children with CP compared to tightly matched controls. While van

Thiel et al. (289) reported no changes in reaction time with increasing target velocities, our CP cohort displayed preserved adaptive motor responses by scaling peak velocities and reducing response latencies during the more challenging high time constraint condition. Importantly, this condition also revealed subtle performance deficits in the preferred arm in CP, extending prior evidence of deficits in the less affected arm in both bilateral (120) and unilateral CP (463, 527). These observation underscore the importance of bilateral assessments and holistic interventions targeting motor deficits within and across limbs for individuals spanning the spectrum of CP diagnoses (1).

While group differences in initial movement angles were not statistically significant in either arm, these angles trended lower in children with CP than controls which may reflect pursuit-based interception strategies (272) or subtle visuomotor impairments that may impede object tracking (528). However, initial movement angles were similarly lower at the high compared to low time constraint condition in both groups, suggesting children with CP retain the ability to adapt motor plans in a task-dependent manner by incorporating target velocity information (270). These findings underscore the dual pattern of coexisting motor deficits and retained motor adaptability that is commonly reported by clinicians working with CP, reinforcing the need for more granular assessments to detect subtle deficits that can inform individualized targeted therapies in this population.

5.4.2. Patterns of PFC activity

In line with our hypothesis, children with CP exhibited suppressed contralateral PFC activity during non-preferred arm interception, consistent with prior reports of attenuated PFC activity in children with CP during physically demanding tasks such as time-constrained reaching (464) and progressive lateral step-up test (135). Diminished PFC activity in CP likely reflects a maladaptive neural resource allocation strategy (298) that is constrained by task context and environmental demands (299), and may contribute to suboptimal functional performance following

brain injury in adulthood (507) or early life (47). Specifically, we propose a task-dependent redistribution of resources away from the rostral prefrontal cortices which mediates higher-order executive functions and action-perception coupling (293, 523), and toward the posterior parieto-occipital and association cortices regulating multisensory and sensorimotor integrative functions (247, 480). We speculate that this redistribution is likely governed by structural and functional constraints imposed by early neural injury, with altered structural and functional connectivity between the prefrontal and motor cortices in CP (351, 353) potentially contributing to their pathologically heightened usage of neural resources for similar levels of motor output as typically developing children (174). Greater magnitude and spatial spread of sensorimotor cortex activity in CP, which scales with the degree of functional impairment and has been linked to abnormal muscle synergies and poor functional outcomes (45, 47, 48), supports our contention that the proposed rostro-caudal redistribution of neural resources in individuals with CP may contribute to, underlie, or exacerbate their observed functional impairments. The context-dependent nature of these proposed adaptations may also explain contradictory reports of exaggerated PFC activity in CP during low-challenge tasks like seated shape-matching (57, 58), and reduced activity during more demanding tasks like time-constrained reaching (464) and the progressive lateral step-up test of functional strength (135).

Altered PFC laterality, observed as ipsilateral dominance in CP compared to contralateral dominance in controls, may reflect disrupted functional specialization of the cerebral hemispheres following early neural damage (529). This hypothesis is supported by preliminary evidence of similar ipsilateral PFC dominance reported in two adults with CP during a unimanual task (352), compared to bilateral PFC dominance observed in controls. While prior work in neurotypical adults suggests a task-dependent dissociation of PFC activity between hemispheres during movement planning (530), the mechanisms underlying altered PFC lateralization in CP remain poorly characterized and warrant further investigation to elucidate their role in mediating aberrant cognitive-motor interactions this group (458).

5.4.3. Relationships between PFC activity and interception performance

While PFC activity metrics were not related to motor performance in either arm in children with CP, negative associations between contralateral PFC activity and interception performance were consistently observed with the preferred arm in typically developing control children. As all but one control participant was right-arm dominant, these negative associations were driven by the left PFC. Similar negative but non-significant trends between left PFC activity and reaching accuracy were previously reported in typically developing children during stationary target reaching (r_s range = -0.453 to -0.020) (464). Prior theories of hemispheric lateralization (531, 532) suggest distinct roles of each hemisphere for motor learning and adaptation in neurotypical adults (531), with the left hemisphere posited to govern typical motor behaviors in stable environments, and the right hemisphere linked with novel behaviors and adaptive responses to perturbations (532). Additionally, visuospatial attention is largely lateralized to the right PFC (533), while exaggerated left PFC activity has been linked both to frustration in typically developing preschoolers (534), and to worse attentional control in children with attention-deficit/hyperactivity disorder (535). While theoretical frameworks of hemispheric specialization in the frontal lobes have not been specified for children, we speculate that excessive left PFC activity may hinder attentional control and emotional regulation, diverting resources from right hemisphere-driven visuospatial attention and adaptive behaviors in novel contexts, leading to impaired motor performance. These findings highlight unique brain-behavior relationship dynamics in typically developing children and those with CP, underscoring the need for considering lateralized PFC functions and their impacts on cognitive-motor interactions in both clinical and neurotypical populations.

5.4.4. Relationships between PFC activity and interception planning

Despite the recognized role of the PFC in motor planning (536), preparedness (245), and prediction (52, 53), this study is the first to quantify the relationships between task-evoked PFC

activity and metrics of motor planning and performance in children with CP and typically developing children. In the non-preferred arm, a direct positive association between contralateral PFC activity and initial movement angles under low time constraints in CP suggests greater PFC activity promotes adaptive motor planning (272) with predictive interception trajectories directed toward an anticipated future target position (30) when task demands are low. Conversely, greater contralateral PFC dominance was related to slower reaction time across time constraints in CP, but to faster reaction time under low time constraints in controls. Controls also exhibited a trend for higher (i.e., less suppressed) contralateral PFC activity than those with CP in the non-preferred arm. Together, these observations suggest complex hemisphere-specific linkages between PFC engagement and motor planning metrics that are dependent on arm and task difficulty. Speculatively, resource allocation between the two PFC hemispheres in CP may involve potential trade-offs between attentional engagement, response speed (i.e., reaction time), and trajectory planning (i.e., initial movement angles) that are influenced by task difficulty and arm used. These findings align with our previous observations (464) that positive relationships between PFC activity and motor accuracy in CP during time-constrained, stationary target reaching similarly varied by arm, task context, and PFC hemisphere, reinforcing the complexity of brain-behavior dynamics following early brain injury. Notably, altered PFC activity reported in more severely affected children with CP following a robot-assisted gait training intervention (56) followed hemisphere-specific patterns, with these changes attributed to improved movement planning abilities following the intensive intervention. The potential for PFC activity metrics to serve as biomarkers for functional improvements in CP underscores the need for further examination aimed at improved characterization of activity patterns in this relatively understudied brain region.

5.5. Limitations

Limited spatial resolution of the fNIRS devices (Portalite, Artinis) used, coupled with the inability of fNIRS to image additional subcortical and deep grey matter structures implicated in

motor control (e.g., basal nuclei) (537), prevented interrogation of the supplementary motor areas (538), parietal-occipital cortices, and cerebellar regions involved in visuomotor integration and multisensory coordination required for successful interception (248, 506, 539). However, despite limited spatial coverage, we successfully captured altered PFC activity patterns in children with CP compared to tightly matched controls. The fNIRS devices also prevented the inclusion of short-separation channels recommended for removing non-neuronal signal contaminants arising from systemic physiological changes (e.g., cardiorespiratory changes in blood pressure, heart rate, respiratory rate) (211, 331). While this device has previously been used to capture PFC hemodynamic in school-aged typically developing children (515, 540), we followed best practice recommendations (399, 402) and prior fNIRS research in CP (46, 135) by incorporating additional principal component analysis (524, 525) during signal processing to remove non-neural signal contaminants. While this approach risks signal overcorrection and increased Type II error via removal of task-evoked, neural hemodynamic signal components (399), we successfully captured group differences in both the magnitude and lateralization of PFC activity. Additional limitations included the inability to conduct detailed sub-group analyses due to our modest sample size and the unavailability of information on brain injury characteristics, visuo-ocular function, or sensory-perceptual abilities in participants with CP. Though prior work revealed a dissociation between sensory function and reaching performance during robotic assessments in children with unilateral CP (17), future studies should include these data for deeper insights into the neurophysiology of sensorimotor interactions in this population.

5.6. Conclusions

Children with CP exhibited pronounced impairments when intercepting moving targets with the non-preferred arm compared to age-, sex-, and race-matched typically developing children, with deficits most apparent when reaching under more challenging high time constraints. Motor deficits were accompanied by atypical PFC activity patterns, with ipsilateral PFC dominance in CP

diverging from contralateral PFC dominance noted in controls, suggesting altered neural reorganization following early brain injury. Contralateral PFC activity and dominance were differently related to metrics of motor planning and performance in children with CP and controls, highlighting distinct brain-behavior relationships underlying interceptive behaviors in each group. These novel observations support the use of multimodal assessment to delineate linkages between neural and behavioral contributors of upper limb dysfunction in CP. Future research aimed at characterizing PFC activity patterns during naturalistic reaching behaviors may identify neural biomarkers that can inform targeted interventions to enhance neuromotor efficiency and optimize motor control, particularly for more impaired arm use in tasks performed under heightened task demands in children with CP.

CHAPTER 6

CONCLUSIONS

This dissertation aimed to characterize brain–behavior relationships underlying upper limb dysfunction in children with CP by integrating high-precision robotic assessments with non-invasive, portable functional neuroimaging during goal-directed behaviors. This novel multimodal approach leveraged the sensitivity of robot-derived kinematic measures and the motion-tolerance of fNIRS to concurrently capture motor behavior and cortical activity during ecologically valid and naturalistic behaviors like reaching and interception. The four complementary studies in this dissertation first describe the feasibility and current use of mobile fNIRS use in CP, then detail how motor planning and execution deficits during goal-directed reaching and interception task vary with task context and relate to clinical tests of manual ability, before finally characterizing PFC activity patterns and their associations to behavioral outcomes across each task. These studies illustrate the potential of integrative approaches to both, illustrate how motor deficits manifest across different task constraints, and offers an assessment framework for probing adaptive or compensatory neural strategies in children with CP, providing empirical foundations for the development of neurophysiology-informed rehabilitation strategies.

The first study used a scoping review methodology to critically appraise and map the current literature on the feasibility and utility of fNIRS to assess cortical activity, functional connectivity, and neuroplasticity in individuals with CP. Our synthesis of 16 studies confirmed that fNIRS offers a viable approach for capturing cortical activation during upper limb tasks children with CP. A small but growing body of literature linked sensorimotor cortical activity to manual ability, with exaggerated or diffuse activation patterns often observed in individuals with poorer

function. Patterns of PFC activity varied by task complexity and cognitive-motor load, with preliminary evidence (59) supporting its potential as a potential biomarker for functional improvements post-intervention. The lack of multimodal studies combining fNIRS with behaviorally demanding motor assessments confirmed a clear scientific gap that served as the conceptual driver for the subsequent empirical studies in this dissertation.

Building on this foundation, the second study used robotic assessments to examine how motor performance and planning deficits in children with CP vary across task contexts and temporal constraints, and detailed their relationship to clinical measures of upper limb function. Children with CP exhibited lower reaching accuracy, increased spatial error, and slower movement velocities compared to age- and sex-matched typically developing children, with deficits accentuated in the non-preferred arm and under high time constraints. Planning impairments were reflected by delayed reaction times and reduced initial movement angles which were relatively consistent across time constraint, suggesting a pervasive disruption in action planning and anticipatory motor control. Importantly, robotic metrics were moderately and directly linked to clinical assessments of manual ability, especially under higher task demands, demonstrating the convergent validity of robotic tools and underscoring their potential to complement clinical evaluations. Notably, the moving target interception task elicited comparable or even superior performance relative to stationary target reaching, highlighting the potential of dynamic, ecologically relevant tasks to uncover latent motor capabilities in children with CP.

The third and fourth studies extended behavioral findings by integrating fNIRS with the robotic tasks to quantify task-evoked PFC activity and its relationship with motor performance. In the stationary target reaching task, PFC activity was suppressed in children with CP during preferred arm movements under high time constraints, while controls showed a non-significant increase in activation magnitude compared to low time constraints, suggesting a potential failure of adaptive PFC upregulation in children with CP under time pressure. Notably, greater PFC activity correlated with higher reaching accuracy in those with CP, particularly in the non-preferred

arm and under high time constraints, supporting the role of the PFC in supporting motor performance when sensorimotor efficiency is compromised. The fourth study further extended this line of inquiry and assessed PFC activity during moving target interception across similarly varied time constraints. Children with CP displayed suppressed contralateral PFC activation and dominance in the non-preferred arm relative to controls, who displayed contralateral PFC dominance. Furthermore, greater contralateral PFC activity and higher ipsilateral PFC dominance in CP was both associated with faster reaction times with the non-preferred arm, raising the possibility of a compensatory, but potentially suboptimal, pattern of PFC recruitment. In contrast, greater contralateral PFC activity and lateralization in controls during preferred arm interception were linked to poorer performance, possibly reflecting neural inefficiency under high demand. These contrasting patterns of associations underscore the importance of interpreting PFC activity in light of behavioral context, task demands, and underlying neural reorganization.

Limitations

This work is subject to several methodological limitations. The constrained spatial resolution of the fNIRS devices (Portalite, Artinis) and the general inability of fNIRS to image subcortical and deep grey matter structures preclude assessment of additional brain areas (e.g., parietal-occipital cortices, cerebellar cortex) that contribute to visuomotor integration and multisensory coordination. The lack of short-separation channels also prevents optimal correction of non-neuronal physiological noise, necessitating the use of alternate signal processing algorithms (principal component analysis) which can introduce signal overcorrection risks. Additionally, our modest sample size lowers sensitivity to detect subtle differences in cortical activity and limits sub-group analyses; however, the inclusion of a carefully matched control group strengthens confidence in the study results. The absence of detailed brain lesion data, visuo-ocular function assessments, and sensory-perceptual measures constrains the scope of our neurophysiological interpretations. Given prior evidence suggesting distinct sensory-motor dissociations in CP (17), future studies

should integrate these measures to further clarify how cortical dynamics influence reaching impairments. Despite these challenges, our findings present a compelling case for adopting multimodal, task-constrained robotic paradigms to assess upper limb function in children with CP.

Major contributions

Taken together, these findings provide critical groundwork for integrating mobile fNIRS with robotic assessments, paving the way for more refined, ecologically valid neuroimaging approaches in CP research. Robotic tools provided reliable and sensitive kinematic metrics that revealed task-specific and limb-specific impairments in both motor execution and planning. When paired with mobile fNIRS, these assessments offered real-time insight into the neurophysiological substrates of behavioral deficits, especially within the PFC region that is central to motor prediction, planning, and anticipatory motor control. These multimodal findings point to three core conclusions:

(1) Upper limb dysfunction in CP is both context-dependent and arm-specific, requiring dynamic assessments that account for environmental and cognitive demands.

(2) The PFC plays a critical yet task-specific role in modulating performance under varying task demands, with aberrant lateralization patterns and reduced adaptability evident in CP.

(3) Integrating cortical and kinematic data can uncover latent compensatory mechanisms or maladaptive strategies that can guide targeted therapeutic interventions aimed at enhancing neuroplasticity and functional recovery.

References

1. Shevell M. Cerebral palsy to cerebral palsy spectrum disorder: Time for a name change? Neurology. 2019;92(5):233-5.

2. Baxter P, Morris C, Rosenbaum P, Paneth N, Leviton A, M. G. The Definition and Classification of Cerebral Palsy. Developmental Medicine & Child Neurology. 2008;49(s2):1-44.

3. Prevention CfDC. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003. MMWR Morb Mortal Wkly Rep. 2004;53(3):57-9.

4. Honeycutt AA, Grosse SD, Dunlap LJ, Schendel DE, Chen H, Brann E, et al. Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment. In: Altman BM, Barnartt SN, Hendershot GE, Larson SA, editors. Using Survey Data to Study Disability: Results from the National Health Survey on Disability. Research in Social Science and Disability. 3: Emerald Group Publishing Limited; 2003. p. 207-28.

5. Arner M, Eliasson AC, Nicklasson S, Sommerstein K, Hägglund G. Hand function in cerebral palsy. Report of 367 children in a population-based longitudinal health care program. J Hand Surg Am. 2008;33(8):1337-47.

6. Mailleux L, Simon-Martinez C, Feys H, Jaspers E. Upper Extremity Movement Pathology during Functional Tasks. In: Müller B, Wolf SI, Brueggemann G-P, Deng Z, McIntosh A, Miller F, et al., editors. Handbook of Human Motion. Cham: Springer International Publishing; 2018. p. 1-18.

7. Pashmdarfard M, Richards LG, Amini M. Factors Affecting Participation of Children with Cerebral Palsy in Meaningful Activities: Systematic Review. Occup Ther Health Care. 2021;35(4):442-79.

8. Steenbergen B, Jongbloed-Pereboom M, Spruijt S, Gordon AM. Impaired motor planning and motor imagery in children with unilateral spastic cerebral palsy: challenges for the future of pediatric rehabilitation. Developmental medicine and child neurology. 2013;55 Suppl 4:43-6.

9. Ickx G, Hatem SM, Riquelme I, Friel KM, Henne C, Araneda R, et al. Impairments of Visuospatial Attention in Children with Unilateral Spastic Cerebral Palsy. Neural Plast. 2018;2018:1435808.

10. Surkar SM, Hoffman RM, Davies B, Harbourne R, Kurz MJ. Impaired anticipatory vision and visuomotor coordination affects action planning and execution in children with hemiplegic cerebral palsy. Res Dev Disabil. 2018;80:64-73.

11. Krumlinde-Sundholm L, Wagner LV. Upper Extremity Assessment and Outcome Evaluation in Cerebral Palsy. In: Miller F, Bachrach S, Lennon N, O'Neil M, editors. Cerebral Palsy. Cham: Springer International Publishing; 2018. p. 1-29.

12. Graser JV, Prospero L, Liesch M, Keller U, van Hedel HJA. Test-retest reliability of upper limb robotic exoskeleton assessments in children and youths with brain lesions. Sci Rep. 2022;12(1):16685.

13. Kuczynski AM, Dukelow SP, Semrau JA, Kirton A. Robotic Quantification of Position Sense in Children With Perinatal Stroke. Neurorehabil Neural Repair. 2016;30(8):762-72.

14. Kuczynski AM, Kirton A, Semrau JA, Dukelow SP. Bilateral reaching deficits after unilateral perinatal ischemic stroke: a population-based case-control study. J Neuroeng Rehabil. 2018;15(1):77.

15. Kuczynski AM, Carlson HL, Lebel C, Hodge JA, Dukelow SP, Semrau JA, et al. Sensory tractography and robot-quantified proprioception in hemiparetic children with perinatal stroke. Hum Brain Mapp. 2017;38(5):2424-40.

16. Kuczynski AM, Dukelow SP, Hodge JA, Carlson HL, Lebel C, Semrau JA, et al. Corticospinal tract diffusion properties and robotic visually guided reaching in children with hemiparetic cerebral palsy. Hum Brain Mapp. 2018;39(3):1130-44.

17. Kuczynski AM, Kirton A, Semrau JA, Dukelow SP. Relative independence of upper limb position sense and reaching in children with hemiparetic perinatal stroke. J Neuroeng Rehabil. 2021;18(1):80.

18. Kuczynski AM, Semrau JA, Kirton A, Dukelow SP. Kinesthetic deficits after perinatal stroke: robotic measurement in hemiparetic children. J Neuroeng Rehabil. 2017;14(1):13.

19. Dehem S, Montedoro V, Brouwers I, Edwards MG, Detrembleur C, Stoquart G, et al. Validation of a robot serious game assessment protocol for upper limb motor impairment in children with cerebral palsy. NeuroRehabilitation. 2019;45(2):137-49.

20. Decraene L, Orban de Xivry JJ, Kleeren L, Crotti M, Verheyden G, Ortibus E, et al. In-depth quantification of bimanual coordination using the Kinarm exoskeleton robot in children with unilateral cerebral palsy. J Neuroeng Rehabil. 2023;20(1):154.

21. Hawe RL, Kuczynski AM, Kirton A, Dukelow SP. Assessment of bilateral motor skills and visuospatial attention in children with perinatal stroke using a robotic object hitting task. J Neuroeng Rehabil. 2020;17(1):18.

22. Hawe RL, Kuczynski AM, Kirton A, Dukelow SP. Robotic assessment of rapid motor decision making in children with perinatal stroke. J Neuroeng Rehabil. 2020;17(1):94.

23. Masia L, Frascarelli F, Morasso P, Di Rosa G, Petrarca M, Castelli E, et al. Reduced short term adaptation to robot generated dynamic environment in children affected by Cerebral Palsy. J Neuroeng Rehabil. 2011;8(1):28.

24. Poitras I, Dukelow SP, Campeau-Lecours A, Mercier C. Robotic assessment of bilateral and unilateral upper limb functions in adults with cerebral palsy. J Neuroeng Rehabil. 2024;21(1):144.

25. Poitras I, Campeau-Lecours A, Mercier C. Relationship between somatosensory and visuo-perceptual impairments and motor functions in adults with hemiparetic cerebral palsy. Front Neurol. 2024;15:1425124.

26. Mazzarella J, McNally M, Richie D, Chaudhari AMW, Buford JA, Pan X, et al. 3D Motion Capture May Detect Spatiotemporal Changes in Pre-Reaching Upper Extremity Movements with and without a Real-Time Constraint Condition in Infants with Perinatal Stroke and Cerebral Palsy: A Longitudinal Case Series. Sensors (Basel). 2020;20(24).

27. Merchant H, Georgopoulos AP. Neurophysiology of perceptual and motor aspects of interception. J Neurophysiol. 2006;95(1):1-13.

28. Merchant H, Zarco W, Prado L, Perez O. Behavioral and neurophysiological aspects of target interception. Adv Exp Med Biol. 2009;629:201-20.

29. Mrotek LA, Soechting JF. Target interception: hand-eye coordination and strategies. J Neurosci. 2007;27(27):7297-309.

30. Savelsbergh GJ, Ledebt A, Smorenburg AR, Deconinck F. Upper limb activity in children with unilateral spastic cerebral palsy: the role of vision in movement strategies. Developmental medicine and child neurology. 2013;55 Suppl 4(s4):38-42.

31. Park K, Ritsma BR, Dukelow SP, Scott SH. A robot-based interception task to quantify upper limb impairments in proprioceptive and visual feedback after stroke. J Neuroeng Rehabil. 2023;20(1):137.

32. Trevarrow MP, Bergwell HE, Groff BR, Wiesman AI, Wilson TW, Kurz MJ. Youth with Cerebral Palsy Display Abnormal Somatosensory Cortical Activity During a Haptic Exploration Task. Neuroscience. 2023;515:53-61.

33. van der Zee YJ, Stiers PLJ, Lagae L, Evenhuis HM. Clinical Assessment of Visual Motion Perception in Children With Brain Damage: A Comparison With Base Rates and Control Sample. Front Hum Neurosci. 2021;15(574):733054.

34. Lust JM, Spruijt S, Wilson PH, Steenbergen B. Motor planning in children with cerebral palsy: A longitudinal perspective. J Clin Exp Neuropsychol. 2018;40(6):559-66.

35. Martinie O, Mercier C, Gordon AM, Robert MT. Upper Limb Motor Planning in Individuals with Cerebral Palsy Aged between 3 and 21 Years Old: A Systematic Review. Brain Sci. 2021;11(7).

36. Steenbergen B, Gordon AM. Activity limitation in hemiplegic cerebral palsy: evidence for disorders in motor planning. Developmental medicine and child neurology. 2006;48(9):780-3.

37. Thomas L, Nam CS. Functional Near-Infrared Spectroscopy (fNIRS) in Neuroergonomics. In: Nam CS, editor. Neuroergonomics. Cognitive Science and Technology. Cham: Springer International Publishing; 2020. p. 53-76.

38. Scholkmann F, Kleiser S, Metz AJ, Zimmermann R, Mata Pavia J, Wolf U, et al. A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. Neuroimage. 2014;85 Pt 1:6-27.

39. von Lühmann A, Zheng Y, Ortega-Martinez A, Kiran S, Somers DC, Cronin-Golomb A, et al. Toward Neuroscience of the Everyday World (NEW) using functional near-infrared spectroscopy. Current opinion in biomedical engineering. 2021;18:100272.

40. Yeung MK. An optical window into brain function in children and adolescents: A systematic review of functional near-infrared spectroscopy studies. Neuroimage. 2021;227:117672.

41. Tian F, Delgado MR, Dhamne SC, Khan B, Alexandrakis G, Romero MI, et al. Quantification of functional near infrared spectroscopy to assess cortical reorganization in children with cerebral palsy. Opt Express. 2010;18(25):25973-86.

42. Hervey N, Khan B, Shagman L, Tian F, Delgado MR, Tulchin-Francis K, et al. Motion tracking and electromyography-assisted identification of mirror hand contributions to functional near-infrared spectroscopy images acquired during a finger-tapping task performed by children with cerebral palsy. Neurophoton. 2014;1(2):025009.

43. Cao J, Khan B, Hervey N, Tian F, Delgado MR, Clegg NJ, et al. Evaluation of cortical plasticity in children with cerebral palsy undergoing constraint-induced movement therapy based on functional near-infrared spectroscopy. J Biomed Opt. 2015;20(4):046009.

44. Khan B, Tian F, Behbehani K, Romero MI, Delgado MR, Clegg NJ, et al. Identification of abnormal motor cortex activation patterns in children with cerebral palsy by functional near-infrared spectroscopy. J Biomed Opt. 2010;15(3):036008.

45. de Campos AC, Sukal-Moulton T, Huppert T, Alter K, Damiano DL. Brain activation patterns underlying upper limb bilateral motor coordination in unilateral cerebral palsy: an fNIRS study. Developmental medicine and child neurology. 2020;62(5):625-32.

46. Kurz MJ, Wilson TW, Arpin DJ. An fNIRS exploratory investigation of the cortical activity during gait in children with spastic diplegic cerebral palsy. Brain and Development. 2014;36(10):870-7.

47. Sukal-Moulton T, de Campos AC, Alter KE, Damiano DL. Functional near-infrared spectroscopy to assess sensorimotor cortical activity during hand squeezing and ankle dorsiflexion in individuals with and without bilateral and unilateral cerebral palsy. Neurophoton. 2020;7(4):045001.

48. Sukal-Moulton T, de Campos AC, Alter KE, Huppert TJ, Damiano DL. Relationship between sensorimotor cortical activation as assessed by functional near infrared spectroscopy and lower extremity motor coordination in bilateral cerebral palsy. Neuroimage Clin. 2018;20:275-85.

49. Sukal-Moulton T, de Campos AC, Stanley CJ, Damiano DL. Functional near infrared spectroscopy of the sensory and motor brain regions with simultaneous kinematic and EMG monitoring during motor tasks. J Vis Exp. 2014(94).

50. Plummer P, Eskes G, Wallace S, Giuffrida C, Fraas M, Campbell G, et al. Cognitive-Motor Interference During Functional Mobility After Stroke: State of the Science and Implications for Future Research. Archives of Physical Medicine and Rehabilitation. 2013;94(12):2565-74.e6.

51. Borra E, Gerbella M, Rozzi S, Tonelli S, Luppino G. Projections to the superior colliculus from inferior parietal, ventral premotor, and ventrolateral prefrontal areas involved in controlling goal-directed hand actions in the macaque. Cereb Cortex. 2014;24(4):1054-65.

52. Fuster JM, Bressler SL. Past makes future: role of pFC in prediction. J Cogn Neurosci. 2015;27(4):639-54.

53. Fuster JM. Prefrontal Executive Functions Predict and Preadapt. Executive Functions in Health and Disease2017. p. 3-19.

54. Martinez-Trujillo J. Visual Attention in the Prefrontal Cortex. Annual Review of Vision Science. 2022;8(1):407-25.

55. Goto K, Hoshi Y, Sata M, Kawahara M, Takahashi M, Murohashi H. Role of the prefrontal cortex in the cognitive control of reaching movements: near-infrared spectroscopy study. J Biomed Opt. 2011;16(12):127003.

56. Perpetuini D, Russo EF, Cardone D, Palmieri R, Filippini C, Tritto M, et al. Identification of Functional Cortical Plasticity in Children with Cerebral Palsy Associated to Robotic-Assisted Gait Training: An fNIRS Study. JCM. 2022;11(22).

57. Surkar SM, Hoffman RM, Harbourne R, Kurz MJ. Neural activation within the prefrontal cortices during the goal-directed motor actions of children with hemiplegic cerebral palsy. Neurophoton. 2018;5(1):011021.

58. Surkar SM, Hoffman RM, Harbourne R, Kurz MJ. Cognitive-Motor Interference Heightens the Prefrontal Cortical Activation and Deteriorates the Task Performance in Children With Hemiplegic Cerebral Palsy. Arch Phys Med Rehabil. 2021;102(2):225-32.

59. Surkar SM, Hoffman RM, Willett S, Flegle J, Harbourne R, Kurz MJ. Hand-Arm Bimanual Intensive Therapy Improves Prefrontal Cortex Activation in Children With Hemiplegic Cerebral Palsy. Pediatr Phys Ther. 2018;30(2):93-100.

60. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.

61. Cazauvieilh J-B. Recherches sur l'agénésie cérébrale et la paralysie congéniale: Imprimerie de Migneret, rue du Dragon, no. 20.; 1827.

62. Barnett R. Cerebral palsy. Lancet. 2018;392(10147):545.

63. Colver AF, Sethumadhavan T. The term diplegia should be abandoned. Archives of Disease in Childhood. 2003;88(4):286-90.

64. Rosenbaum PL, Dan B. The continuing evolution of "Cerebral Palsy". Ann Phys Rehabil Med. 2020;63(5):387-8.

65. Chabrier S, Pouyfaucon M, Chatelin A, Bleyenheuft Y, Fluss J, Gautheron V, et al. From congenial paralysis to post-early brain injury developmental condition: Where does cerebral palsy actually stand? Ann Phys Rehabil Med. 2020;63(5):431-8.

66. Baxter P. For and against the term cerebral palsy. Developmental medicine and child neurology. 2015;57(7):592.

67. Shusterman M. Introducing the term 'early developmental brain injury/interference' and a new framework for discussing cerebral palsy. Developmental medicine and child neurology. 2015;57(2):110-1.

68. Korzeniewski SJ, Slaughter J, Lenski M, Haak P, Paneth N. The complex aetiology of cerebral palsy. Nature Reviews Neurology. 2018;14(9):528-43.

69. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2(1):15082.

70. Sadowska M, Sarecka-Hujar B, Kopyta I. Cerebral Palsy: Current Opinions on Definition, Epidemiology, Risk Factors, Classification and Treatment Options. Neuropsychiatr Dis Treat. 2020;16:1505-18.

71. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. Am J Obstet Gynecol. 2015;213(6):779-88.

72. Leviton A, Fichorova RN, O'Shea TM, Kuban K, Paneth N, Dammann O, et al. Two-hit model of brain damage in the very preterm newborn: small for gestational age and postnatal systemic inflammation. Pediatr Res. 2013;73(3):362-70.

73. Durkin MS, Maenner MJ, Benedict RE, Van Naarden Braun K, Christensen D, Kirby RS, et al. The role of socio-economic status and perinatal factors in racial disparities in the risk of cerebral palsy. Developmental medicine and child neurology. 2015;57(9):835-43.

74. Murugasen S, Springer P, Olusanya BO, Gladstone M, Newton C, Kakooza-Mwesige A, et al. Cerebral palsy in African paediatric populations: A scoping review. Developmental medicine and child neurology. 2024;66(8):990-1012.

75. McIntyre S, Goldsmith S, Webb A, Ehlinger V, Hollung SJ, McConnell K, et al. Global prevalence of cerebral palsy: A systematic analysis. Developmental medicine and child neurology. 2022;64(12):1494-506.

76. Horber V, Andersen GL, Arnaud C, De La Cruz J, Dakovic I, Greitane A, et al. Prevalence, Clinical Features, Neuroimaging, and Genetic Findings in Children With Ataxic Cerebral Palsy in Europe. Neurology. 2023;101(24):e2509-e21.

77. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed. 2008;93(2):F153-61.

78. Li Y, Wisnowski JL, Chalak L, Mathur AM, McKinstry RC, Licona G, et al. Mild hypoxic-ischemic encephalopathy (HIE): timing and pattern of MRI brain injury. Pediatr Res. 2022;92(6):1731-6.

79. Dunbar M, Kirton A. Perinatal Stroke. Semin Pediatr Neurol. 2019;32:100767.

80. Sporns PB, Fullerton HJ, Lee S, Kim H, Lo WD, Mackay MT, et al. Childhood stroke. Nature Reviews Disease Primers. 2022;8(1):12.

81. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res. 2001;50(5):553-62.

82. Pons R, Vanezis A, Skouteli H, Papavasiliou A, Tziomaki M, Syrengelas D, et al. Upper Limb Function, Kinematic Analysis, and Dystonia Assessment in Children With Spastic Diplegic Cerebral Palsy and Periventricular Leukomalacia. J Child Neurol. 2017;32(11):936-41.

83. Papadimitriou I, Dalivigka Z, Outsika C, Scarmeas N, Pons R. Dystonia assessment in children with cerebral palsy and periventricular leukomalacia. Eur J Paediatr Neurol. 2021;32:8-15.

84. Cioni G, Sales B, Paolicelli PB, Petacchi E, Scusa MF, Canapicchi R. MRI and clinical characteristics of children with hemiplegic cerebral palsy. Neuropediatrics. 1999;30(5):249-55.

85. Fernandez-Lopez D, Natarajan N, Ashwal S, Vexler ZS. Mechanisms of perinatal arterial ischemic stroke. J Cereb Blood Flow Metab. 2014;34(6):921-32.

86. Kirton A, Deveber G. Life after perinatal stroke. Stroke. 2013;44(11):3265-71.

87. Kirton A, deVeber G. Advances in perinatal ischemic stroke. Pediatr Neurol. 2009;40(3):205-14.

88. Kirton A, Deveber G, Pontigon AM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann Neurol. 2008;63(4):436-43.

89. Núñez C, Arca G, Agut T, Stephan-Otto C, García-Alix A. Precise neonatal arterial ischemic stroke classification with a three-dimensional map of the arterial territories of the neonatal brain. Pediatr Res. 2020;87(7):1231-6.

90. Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2004;62(6):851-63.

91. Reid SM, Dagia CD, Ditchfield MR, Carlin JB, Reddihough DS. Population-based studies of brain imaging patterns in cerebral palsy. Developmental medicine and child neurology. 2014;56(3):222-32.

92. Towsley K, Shevell MI, Dagenais L, Consortium R. Population-based study of neuroimaging findings in children with cerebral palsy. Eur J Paediatr Neurol. 2011;15(1):29-35.

93. Elliott D. The Legacy of the Kennard Principle. J Undergrad Neurosci Educ. 2020;19(1):R11-r4.

94. Kennard MA. Age and other factors in motor recovery from precentral lesions in monkeys. American Journal of Physiology. 1936;115(1):138-46.

95. de Almeida Carvalho Duarte N, Collange Grecco LA, Zanon N, Galli M, Fregni F, Santos Oliveira C. Motor Cortex Plasticity in Children With Spastic Cerebral Palsy: A Systematic Review. J Mot Behav. 2017;49(4):355-64.

96. Eyre JA. Corticospinal tract development and its plasticity after perinatal injury. Neuroscience & Biobehavioral Reviews. 2007;31(8):1136-49.

97. Kirton A. Modeling developmental plasticity after perinatal stroke: defining central therapeutic targets in cerebral palsy. Pediatr Neurol. 2013;48(2):81-94.

98. Kirton A, Metzler MJ, Craig BT, Hilderley A, Dunbar M, Giuffre A, et al. Perinatal stroke: mapping and modulating developmental plasticity. Nat Rev Neurol. 2021;17(7):415-32.

99. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. Arch Phys Med Rehabil. 1989;70(2):144-55.

100. Lance JW. What is spasticity? Lancet. 1990;335(8689):606.

101. Sheean G. Neurophysiology of spasticity. In: Barnes MP, Johnson GR, editors. Upper Motor Neurone Syndrome and Spasticity: Clinical Management and Neurophysiology. 2 ed. Cambridge: Cambridge University Press; 2008. p. 9-63.

102. Bar-On L, Molenaers G, Aertbelien E, Van Campenhout A, Feys H, Nuttin B, et al. Spasticity and its contribution to hypertonia in cerebral palsy. Biomed Res Int. 2015;2015:317047.

103. Damiano DL, Dodd K, Taylor NF. Should we be testing and training muscle strength in cerebral palsy? Developmental medicine and child neurology. 2002;44(1):68-72.

104. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW, Task Force on Childhood Motor D. Classification and definition of disorders causing hypertonia in childhood. Pediatrics. 2003;111(1):e89-97.

105. Monbaliu E, Himmelmann K, Lin JP, Ortibus E, Bonouvrie L, Feys H, et al. Clinical presentation and management of dyskinetic cerebral palsy. Lancet Neurol. 2017;16(9):741-9.

106. Sanger TD, Chen D, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW, et al. Definition and classification of negative motor signs in childhood. Pediatrics. 2006;118(5):2159-67.

107. Damiano DL. Activity, activity, activity: rethinking our physical therapy approach to cerebral palsy. Phys Ther. 2006;86(11):1534-40.

108. Damiano DL, Martellotta TL, Sullivan DJ, Granata KP, Abel MF. Muscle force production and functional performance in spastic cerebral palsy: relationship of cocontraction. Arch Phys Med Rehabil. 2000;81(7):895-900.

109. Moreau NG, Falvo MJ, Damiano DL. Rapid force generation is impaired in cerebral palsy and is related to decreased muscle size and functional mobility. Gait & Posture. 2012;35(1):154-8.

110. Wiley ME, Damiano DL. Lower-extremity strength profiles in spastic cerebral palsy. Developmental medicine and child neurology. 1998;40(2):100-7.

111. Brun C, Traverse E, Granger E, Mercier C. Somatosensory deficits and neural correlates in cerebral palsy: a scoping review. Developmental medicine and child neurology. 2021;63(12):1382-93.

112. Ego A, Lidzba K, Brovedani P, Belmonti V, Gonzalez-Monge S, Boudia B, et al. Visual–perceptual impairment in children with cerebral palsy: a systematic review. Developmental Medicine & Child Neurology. 2015;57(s2):46-51.

113. Klingels K, Demeyere I, Jaspers E, De Cock P, Molenaers G, Boyd R, et al. Upper limb impairments and their impact on activity measures in children with unilateral cerebral palsy. Eur J Paediatr Neurol. 2012;16(5):475-84.

114. Hoon AH, Jr., Stashinko EE, Nagae LM, Lin DD, Keller J, Bastian A, et al. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. Developmental medicine and child neurology. 2009;51(9):697-704.

115. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics. 2012;130(5):e1285-312.

116. Arnould C, Penta M, Thonnard JL. Hand impairments and their relationship with manual ability in children with cerebral palsy. Journal of Rehabilitation Medicine. 2007;39(9):708-14.

117. Burgess A, Boyd RN, Chatfield MD, Ziviani J, Wotherspoon J, Sakzewski L. Hand function and self-care in children with cerebral palsy. Developmental medicine and child neurology. 2021;63(5):576-83.

118. Russo RN, Skuza PP, Sandelance M, Flett P. Upper limb impairments, process skills, and outcome in children with unilateral cerebral palsy. Developmental medicine and child neurology. 2019;61(9):1080-6.

119. Amini M, Saneii SH, Pashmdarfard M. Factors affecting social participation of Iranian children with cerebral palsy. Occup Ther Health Care. 2018;32(3):290-305.

120. Makki D, Duodu J, Nixon M. Prevalence and pattern of upper limb involvement in cerebral palsy. J Child Orthop. 2014;8(3):215-9.

121. Visicato LP, da Costa CS, Damasceno VA, de Campos AC, Rocha NA. Evaluation and characterization of manual reaching in children with cerebral palsy: A systematic review. Res Dev Disabil. 2015;36C:162-74.

122. Arnould C, Penta M, Renders A, Thonnard JL. ABILHAND-Kids: a measure of manual ability in children with cerebral palsy. Neurology. 2004;63(6):1045-52.

123. Ziviani J, Poulsen AA, Cuskelly M. Understanding motivation in the context of engaging children in therapy. In: Jenny Ziviani AP, and Monica Cuskelly, editor. The art and science of motivation: a therapist's guide to working with children: Jessica Kingsley Publishers; 2013. p. 23-57.

124. Miller L, Ziviani J, Ware RS, Boyd RN. Does Context Matter? Mastery Motivation and Therapy Engagement of Children with Cerebral Palsy. Phys Occup Ther Pediatr. 2016;36(2):155-70.

125. Miller L, Ziviani J, Ware RS, Boyd RN. Mastery motivation as a predictor of occupational performance following upper limb intervention for school-aged children with congenital hemiplegia. Developmental medicine and child neurology. 2014;56(10):976-83.

126. Adler C, Berweck S, Lidzba K, Becher T, Staudt M. Mirror movements in unilateral spastic cerebral palsy: Specific negative impact on bimanual activities of daily living. Eur J Paediatr Neurol. 2015;19(5):504-9.

127. Utley A, Steenbergen B. Discrete bimanual co-ordination in children and young adolescents with hemiparetic cerebral palsy: recent findings, implications and future research directions. Pediatr Rehabil. 2006;9(2):127-36.

128. Verhage CH, Groenendaal F, van der Net J, van Schooneveld MMJ, de Vries LS, van der Aa NE. Bimanual performance in children with unilateral perinatal arterial ischaemic stroke or periventricular haemorrhagic infarction. European Journal of Paediatric Neurology. 2022;37:46-52.

129. Mailleux L, Simon-Martinez C, Radwan A, Blommaert J, Gooijers J, Wenderoth N, et al. White matter characteristics of motor, sensory and interhemispheric tracts underlying impaired upper limb function in children with unilateral cerebral palsy. Brain Struct Funct. 2020;225(5):1495-509.

130. Qin Y, Sun B, Zhang H, Li Y, Zhang T, Luo C, et al. Aberrant Interhemispheric Functional Organization in Children with Dyskinetic Cerebral Palsy. Biomed Res Int. 2019;2019:4362539.

131. Eyre JA, Smith M, Dabydeen L, Clowry GJ, Petacchi E, Battini R, et al. Is hemiplegic cerebral palsy equivalent to amblyopia of the corticospinal system? Ann Neurol. 2007;62(5):493-503.

132. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-56.

133. Houwink A, Aarts PBM, Geurts ACH, Steenbergen B. A neurocognitive perspective on developmental disregard in children with hemiplegic cerebral palsy. Research in Developmental Disabilities. 2011;32(6):2157-63.

134. Zielinski IM, Jongsma ML, Baas CM, Aarts PB, Steenbergen B. Unravelling developmental disregard in children with unilateral cerebral palsy by measuring event-related potentials during a simple and complex task. BMC Neurol. 2014;14(1):6.

135. Licea J, Khan OA, Singh T, Modlesky CM. Prefrontal cortex hemodynamic activity during a test of lower extremity functional muscle strength in children with cerebral palsy: A functional near-infrared spectroscopy study. Eur J Neurosci. 2024;59(2):298-307.

136. Gordon AM, Bleyenheuft Y, Steenbergen B. Pathophysiology of impaired hand function in children with unilateral cerebral palsy. Developmental medicine and child neurology. 2013;55 Suppl 4:32-7.

137. Friel KM, Chakrabarty S, Martin JH. Pathophysiological mechanisms of impaired limb use and repair strategies for motor systems after unilateral injury of the developing brain. Developmental medicine and child neurology. 2013;55 Suppl 4:27-31.

138. Eyre JA, Miller S, Clowry GJ, Conway EA, Watts C. Functional corticospinal projections are established prenatally in the human foetus permitting involvement in the development of spinal motor centres. Brain. 2000;123 (Pt 1):51-64.

139. Eyre JA, Taylor JP, Villagra F, Smith M, Miller S. Evidence of activity-dependent withdrawal of corticospinal projections during human development. Neurology. 2001;57(9):1543-54.

140. Staudt M, Gerloff C, Grodd W, Holthausen H, Niemann G, Krageloh-Mann I. Reorganization in congenital hemiparesis acquired at different gestational ages. Ann Neurol. 2004;56(6):854-63.

141. Lemon RN. Descending pathways in motor control. Annu Rev Neurosci. 2008;31(Volume 31, 2008):195-218.

142. Jaspers E, Byblow WD, Feys H, Wenderoth N. The Corticospinal Tract: A Biomarker to Categorize Upper Limb Functional Potential in Unilateral Cerebral Palsy. Front Pediatr. 2015;3:112.

143. Staudt M. Brain plasticity following early life brain injury: insights from neuroimaging. Semin Perinatol. 2010;34(1):87-92.

144. Staudt M, Grodd W, Gerloff C, Erb M, Stitz J, Krageloh-Mann I. Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. Brain. 2002;125(Pt 10):2222-37.

145. Thickbroom GW, Byrnes ML, Archer SA, Nagarajan L, Mastaglia FL. Differences in sensory and motor cortical organization following brain injury early in life. Ann Neurol. 2001;49(3):320-7.

146. Wilke M, Staudt M, Juenger H, Grodd W, Braun C, Krageloh-Mann I. Somatosensory system in two types of motor reorganization in congenital hemiparesis: topography and function. Hum Brain Mapp. 2009;30(3):776-88.

147. Guzzetta A, Bonanni P, Biagi L, Tosetti M, Montanaro D, Guerrini R, et al. Reorganisation of the somatosensory system after early brain damage. Clin Neurophysiol. 2007;118(5):1110-21.

148. Kostovic I, Jovanov-Milosevic N. The development of cerebral connections during the first 20-45 weeks' gestation. Semin Fetal Neonatal Med. 2006;11(6):415-22.

149. Knijnenburg ACS, Steinbusch CVM, Janssen-Potten YJM, Defesche A, Vermeulen RJ. Neuro-imaging characteristics of sensory impairment in cerebral palsy; a systematic review. Front Rehabil Sci. 2023;4:1084746.

150. Mailleux L, Klingels K, Fiori S, Simon-Martinez C, Demaerel P, Locus M, et al. How does the interaction of presumed timing, location and extent of the underlying brain lesion relate to upper limb function in children with unilateral cerebral palsy? Eur J Paediatr Neurol. 2017;21(5):763-72.

151. Feys H, Eyssen M, Jaspers E, Klingels K, Desloovere K, Molenaers G, et al. Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. Eur J Paediatr Neurol. 2010;14(2):169-77.

152. Holmefur M, Kits A, Bergstrom J, Krumlinde-Sundholm L, Flodmark O, Forssberg H, et al. Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy. Neurorehabil Neural Repair. 2013;27(1):72-8.

153. Pagnozzi AM, Fiori S, Boyd RN, Guzzetta A, Doecke J, Gal Y, et al. Optimization of MRI-based scoring scales of brain injury severity in children with unilateral cerebral palsy. Pediatr Radiol. 2016;46(2):270-9.

154. Dinomais M, Hertz-Pannier L, Groeschel S, Delion M, Husson B, Kossorotoff M, et al. Does Contralesional Hand Function After Neonatal Stroke Only Depend on Lesion Characteristics? Stroke. 2016;47(6):1647-50.

155. Rose S, Guzzetta A, Pannek K, Boyd R. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. Brain Connect. 2011;1(4):309-16.

156. Tsao H, Pannek K, Boyd RN, Rose SE. Changes in the integrity of thalamocortical connections are associated with sensorimotor deficits in children with congenital hemiplegia. Brain Struct Funct. 2015;220(1):307-18.

157. Weinstein M, Green D, Rudisch J, Zielinski IM, Benthem-Muniz M, Jongsma MLA, et al. Understanding the relationship between brain and upper limb function in children with unilateral motor impairments: A multimodal approach. Eur J Paediatr Neurol. 2018;22(1):143-54.

158. Hill NM, Malone LA, Sun LR. Stroke in the Developing Brain: Neurophysiologic Implications of Stroke Timing, Location, and Comorbid Factors. Pediatr Neurol. 2023;148:37-43.

159. Craig BT, Hilderley A, Kirton A, Carlson HL. Imaging Developmental and Interventional Plasticity Following Perinatal Stroke. Can J Neurol Sci. 2021;48(2):157-71.

160. Gaberova K, Pacheva I, Timova E, Petkova A, Velkova K, Ivanov I. An Individualized Approach to Neuroplasticity After Early Unilateral Brain Damage. Front Psychiatry. 2019;10:747.

161. Damiano DL. Meaningfulness of mean group results for determining the optimal motor rehabilitation program for an individual child with cerebral palsy. Developmental medicine and child neurology. 2014;56(12):1141-6.

162. Azhari A, Truzzi A, Neoh MJ, Balagtas JPM, Tan HH, Goh PP, et al. A decade of infant neuroimaging research: What have we learned and where are we going? Infant Behav Dev. 2020;58:101389.

163. Gaberova K, Pacheva I, Ivanov I. Task-related fMRI in hemiplegic cerebral palsy-A systematic review. J Eval Clin Pract. 2018;24(4):839-50.

164. Vandermeeren Y, Sebire G, Grandin CB, Thonnard JL, Schlogel X, De Volder AG. Functional reorganization of brain in children affected with congenital hemiplegia: fMRI study. Neuroimage. 2003;20(1):289-301.

165. Vallinoja J, Nurmi T, Jaatela J, Wens V, Bourguignon M, Maenpaa H, et al. Functional connectivity of sensorimotor network is enhanced in spastic diplegic cerebral palsy: A multimodal study using fMRI and MEG. Clin Neurophysiol. 2024;157:4-14.

166. Reid LB, Boyd RN, Cunnington R, Rose SE. Interpreting Intervention Induced Neuroplasticity with fMRI: The Case for Multimodal Imaging Strategies. Neural Plast. 2016;2016:2643491.

167. Woodward KE, Carlson HL, Kuczynski A, Saunders J, Hodge J, Kirton A. Sensory-motor network functional connectivity in children with unilateral cerebral palsy secondary to perinatal stroke. Neuroimage Clin. 2019;21:101670.

168. Lee-Park JJ, Deshpande H, Lisinski J, LaConte S, Ramey S, DeLuca S. Neuroimaging Strategies Addressing Challenges in Using fMRI for the Children with Cerebral Palsy. Journal of Behavioral and Brain Science. 2018;08(05):306-18.

169. Altman NR, Bernal B. Pediatric applications of functional magnetic resonance imaging. Pediatr Radiol. 2015;45 Suppl 3:S382-96.

170. Tajik-Parvinchi DJ, Black KR, Roudbarani F, Weiss JA, King G. Functional magnetic resonance imaging (fMRI) in typical and atypical brain development: Challenges and suggestions. In: Halpern-Felsher B, editor. Encyclopedia of Child and Adolescent Health. Oxford: Academic Press; 2023. p. 4-13.

171. Demas J, Bourguignon M, Perivier M, De Tiege X, Dinomais M, Van Bogaert P. Mu rhythm: State of the art with special focus on cerebral palsy. Ann Phys Rehabil Med. 2020;63(5):439-46.

172. Inuggi A, Bassolino M, Tacchino C, Pippo V, Bergamaschi V, Campus C, et al. Ipsilesional functional recruitment within lower mu band in children with unilateral cerebral palsy, an event-related desynchronization study. Exp Brain Res. 2018;236(2):517-27.

173. Kukke SN, de Campos AC, Damiano D, Alter KE, Patronas N, Hallett M. Cortical activation and inter-hemispheric sensorimotor coherence in individuals with arm dystonia due to childhood stroke. Clin Neurophysiol. 2015;126(8):1589-98.

174. Short MR, Damiano DL, Kim Y, Bulea TC. Children With Unilateral Cerebral Palsy Utilize More Cortical Resources for Similar Motor Output During Treadmill Gait. Front Hum Neurosci. 2020;14:36.

175. VerMaas JR, Lew BJ, Trevarrow MP, Wilson TW, Kurz MJ. Children with Cerebral Palsy Have Altered Occipital Cortical Oscillations during a Visuospatial Attention Task. Cereb Cortex. 2021;31(7):3353-62.

176. Hoffman RM, Embury CM, Lew BJ, Heinrichs-Graham E, Wilson TW, Kurz MJ. Cortical oscillations that underlie visual selective attention are abnormal in adolescents with cerebral palsy. Sci Rep. 2021;11(1):4661.

177. VerMaas JR, Embury CM, Hoffman RM, Trevarrow MP, Wilson TW, Kurz MJ. Beyond the eye: Cortical differences in primary visual processing in children with cerebral palsy. Neuroimage Clin. 2020;27:102318.

178. Kurz MJ, Heinrichs-Graham E, Becker KM, Wilson TW. The magnitude of the somatosensory cortical activity is related to the mobility and strength impairments seen in children with cerebral palsy. J Neurophysiol. 2015;113(9):3143-50.

179. Hinton EH, Busboom MT, Embury CM, Spooner RK, Wilson TW, Kurz MJ. Adults with cerebral palsy exhibit uncharacteristic cortical oscillations during an adaptive sensorimotor control task. Sci Rep. 2024;14(1):10788.

180. Kurz MJ, Becker KM, Heinrichs-Graham E, Wilson TW. Neurophysiological abnormalities in the sensorimotor cortices during the motor planning and movement

execution stages of children with cerebral palsy. Developmental medicine and child neurology. 2014;56(11):1072-7.

181. Bergwell H, Trevarrow M, Corr B, Baker S, Reelfs H, Wilson TW, et al. Power training alters somatosensory cortical activity of youth with cerebral palsy. Ann Clin Transl Neurol. 2022;9(5):659-68.

182. Busboom M, Corr B, Reelfs A, Trevarrow M, Reelfs H, Baker S, et al. Therapeutic Lower Extremity Power Training Alters the Sensorimotor Cortical Activity of Individuals With Cerebral Palsy. Arch Rehabil Res Clin Transl. 2022;4(1):100180.

183. Jacobs NPT, Pouwels PJW, van der Krogt MM, Meyns P, Zhu K, Nelissen L, et al. Brain structural and functional connectivity and network organization in cerebral palsy: A scoping review. Developmental medicine and child neurology. 2023;65(9):1157-73.

184. Kotsoni E, Byrd D, Casey BJ. Special considerations for functional magnetic resonance imaging of pediatric populations. J Magn Reson Imaging. 2006;23(6):877-86.

185. Raschle NM, Lee M, Buechler R, Christodoulou JA, Chang M, Vakil M, et al. Making MR imaging child's play - pediatric neuroimaging protocol, guidelines and procedure. J Vis Exp. 2009(29).

186. Wilke M, Groeschel S, Lorenzen A, Rona S, Schuhmann MU, Ernemann U, et al. Clinical application of advanced MR methods in children: points to consider. Ann Clin Transl Neurol. 2018;5(11):1434-55.

187. Nebel MB, Lidstone DE, Wang L, Benkeser D, Mostofsky SH, Risk BB. Accounting for motion in resting-state fMRI: What part of the spectrum are we characterizing in autism spectrum disorder? Neuroimage. 2022;257:119296.

188. Khan OA, Rahman S, Baduni K, Modlesky CM. Assessment of cortical activity, functional connectivity, and neuroplasticity in cerebral palsy using functional near-infrared spectroscopy: A scoping review. Developmental medicine and child neurology. 2025;67(00):1–17.

189. Zhang F, Roeyers H. Exploring brain functions in autism spectrum disorder: A systematic review on functional near-infrared spectroscopy (fNIRS) studies. Int J Psychophysiol. 2019;137:41-53.

190. Conti E, Scaffei E, Bosetti C, Marchi V, Costanzo V, Dell'Oste V, et al. Looking for "fNIRS Signature" in Autism Spectrum: A Systematic Review Starting From Preschoolers. Front Neurosci. 2022;16:785993.

191. Sun W, Wu X, Zhang T, Lin F, Sun H, Li J. Narrowband Resting-State fNIRS Functional Connectivity in Autism Spectrum Disorder. Frontiers in Human Neuroscience. 2021;15.

192. Da C, Jj L, Metting Z, Se R, Jm S, Jwj E, et al. The feasibility of fNIRS as a diagnostic tool for pediatric TBI: A pilot study. Eur J Paediatr Neurol. 2021;30:22-4.

193. Xu SY, Lu FM, Wang MY, Hu ZS, Zhang J, Chen ZY, et al. Altered Functional Connectivity in the Motor and Prefrontal Cortex for Children With Down's Syndrome: An fNIRS Study. Front Hum Neurosci. 2020;14(6):6.

194. Gosse LK, Bell SW, Hosseini SMH. Functional near-infrared spectroscopy in developmental psychiatry: a review of attention deficit hyperactivity disorder. Eur Arch Psychiatry Clin Neurosci. 2022;272(2):273-90.

195. Huneau C, Benali H, Chabriat H. Investigating Human Neurovascular Coupling Using Functional Neuroimaging: A Critical Review of Dynamic Models. Front Neurosci. 2015;9:467.

196. Kozberg M, Hillman E. Chapter 10 - Neurovascular coupling and energy metabolism in the developing brain. In: Masamoto K, Hirase H, Yamada K, editors. Progress in Brain Research. 225: Elsevier; 2016. p. 213-42.

197. Hillman EM. Coupling mechanism and significance of the BOLD signal: a status report. Annu Rev Neurosci. 2014;37(1):161-81.

198. Obrig H, Villringer A. Beyond the visible--imaging the human brain with light. J Cereb Blood Flow Metab. 2003;23(1):1-18.

199. Oshina I, Spigulis J. Beer-Lambert law for optical tissue diagnostics: current state of the art and the main limitations. J Biomed Opt. 2021;26(10):100901.

200. Cutini S, Moro SB, Bisconti S. Functional near infrared optical imaging in cognitive neuroscience: an introductory review. Journal of near Infrared Spectroscopy. 2012;20(1):75-92.

201. Pinti P, Aichelburg C, Gilbert S, Hamilton A, Hirsch J, Burgess P, et al. A Review on the Use of Wearable Functional Near-Infrared Spectroscopy in Naturalistic Environments(). Jpn Psychol Res. 2018;60(4):347-73.

202. Balardin JB, Zimeo Morais GA, Furucho RA, Trambaiolli L, Vanzella P, Biazoli C, Jr., et al. Imaging Brain Function with Functional Near-Infrared Spectroscopy in Unconstrained Environments. Front Hum Neurosci. 2017;11:258.

203. Tan SS, van Gorp M, Voorman JM, Geytenbeek JJ, Reinders-Messelink HA, Ketelaar M, et al. Development curves of communication and social interaction in individuals with cerebral palsy. Developmental medicine and child neurology. 2020;62(1):132-9.

204. Harniess PA, Gibbs D, Bezemer J, Purna Basu A. Parental engagement in early intervention for infants with cerebral palsy-A realist synthesis. Child Care Health Dev. 2022;48(3):359-77.

205. Paulmurugan K, Vijayaragavan V, Ghosh S, Padmanabhan P, Gulyás B. Brain–Computer Interfacing Using Functional Near-Infrared Spectroscopy (fNIRS). Biosensors [Internet]. 2021; 11(10).

206. Orlandi S, House SC, Karlsson P, Saab R, Chau T. Brain-Computer Interfaces for Children With Complex Communication Needs and Limited Mobility: A Systematic Review. Front Hum Neurosci. 2021;15:643294.

207. Hoshi Y, Yamada Y. Overview of diffuse optical tomography and its clinical applications. J Biomed Opt. 2016;21(9):091312.

208. Crawford SB, Le TC, Bowden AK. Customizable optode attachments to improve hair clearance timing and inclusiveness in functional near-infrared spectroscopy research. Neurophoton. 2024;11(4):045011.

209. Lloyd-Fox S, Blasi A, McCann S, Rozhko M, Katus L, Mason L, et al. Habituation and novelty detection fNIRS brain responses in 5- and 8-month-old infants: The Gambia and UK. Dev Sci. 2019;22(5):e12817.

210. Pinti P, Cardone D, Merla A. Simultaneous fNIRS and thermal infrared imaging during cognitive task reveal autonomic correlates of prefrontal cortex activity. Scientific Reports. 2015;5(1):17471.

211. Tachtsidis I, Scholkmann F. False positives and false negatives in functional near-infrared spectroscopy: issues, challenges, and the way forward. Neurophoton. 2016;3(3):031405.

212. Yücel MA, Selb J, Aasted CM, Petkov MP, Becerra L, Borsook D, et al. Short separation regression improves statistical significance and better localizes the hemodynamic response obtained by near-infrared spectroscopy for tasks with differing autonomic responses. Neurophoton. 2015;2(3):035005.

213. Kwasa J, Peterson HM, Karrobi K, Jones L, Parker T, Nickerson N, et al. Demographic reporting and phenotypic exclusion in fNIRS. Front Neurosci. 2023;17:1086208.

214. Parker TC, Ricard JA. Structural racism in neuroimaging: perspectives and solutions. Lancet Psychiatry. 2022;9(5):e22.

215. Louis CC, Webster CT, Gloe LM, Moser JS. Hair me out: Highlighting systematic exclusion in psychophysiological methods and recommendations to increase inclusion. Front Hum Neurosci. 2022;16:1058953.

216. Brew N, Walker D, Wong FY. Cerebral vascular regulation and brain injury in preterm infants. Am J Physiol Regul Integr Comp Physiol. 2014;306(11):R773-86.

217. Kratzer I, Chip S, Vexler ZS. Barrier mechanisms in neonatal stroke. Front Neurosci. 2014;8:359.

218. Hoshi Y. Hemodynamic signals in fNIRS. In: Masamoto K, Hirase H, Yamada K, editors. Progress in Brain Research. 225: Elsevier; 2016. p. 153-79.

219. Schiariti V, Klassen AF, Cieza A, Sauve K, O'Donnell M, Armstrong R, et al. Comparing contents of outcome measures in cerebral palsy using the International Classification of Functioning (ICF-CY): a systematic review. Eur J Paediatr Neurol. 2014;18(1):1-12.

220. Hao Y, Bala K, McRae M, Carnahan H, Borschel GH, Ho ES. Establishing expert consensus on the evaluation of pediatric upper extremity function. J Hand Ther. 2015;28(2):151-6; quiz 7.

221. Eliasson AC, Krumlinde-Sundholm L, Rosblad B, Beckung E, Arner M, Ohrvall AM, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. Developmental medicine and child neurology. 2006;48(7):549-54.

222. Öhrvall AM, Eliasson AC. Parents' and therapists' perceptions of the content of the Manual Ability Classification System, MACS. Scand J Occup Ther. 2010;17(3):209-16.

223. Rosenbaum P, Eliasson AC, Hidecker MJ, Palisano RJ. Classification in childhood disability: focusing on function in the 21st century. J Child Neurol. 2014;29(8):1036-45.

224. Grampurohit N, Mulcahey MJ. Outcome Measures. Pediatric Hand Therapy: Elsevier; 2020. p. 31-56.

225. Mathiowetz V, Federman S, Wiemer D. Box and Block Test of Manual Dexterity: Norms for 6–19 Year Olds. Canadian Journal of Occupational Therapy. 1985;52(5):241-5.

226. Jongbloed-Pereboom M, Nijhuis-van der Sanden MW, Steenbergen B. Norm scores of the box and block test for children ages 3-10 years. Am J Occup Ther. 2013;67(3):312-8.

227. Araneda R, Ebner-Karestinos D, Paradis J, Saussez G, Friel KM, Gordon AM, et al. Reliability and responsiveness of the Jebsen-Taylor Test of Hand Function and the Box and Block Test for children with cerebral palsy. Developmental medicine and child neurology. 2019;61(10):1182-8.

228. Liang K-J, Chen H-L, Shieh J-Y, Wang T-N. Measurement properties of the box and block test in children with unilateral cerebral palsy. Scientific Reports. 2021;11(1):20955.

229. Mathiowetz V, Rogers SL, Dowe-Keval M, Donahoe L, Rennells C. The Purdue Pegboard: norms for 14- to 19-year-olds. Am J Occup Ther. 1986;40(3):174-9.

230. Gardner RA, Broman M. The Purdue pegboard: Normative data on 1334 school children. Journal of Clinical Child Psychology. 1979;8(3):156-62.

231. Bakhshipour E, Koiler R, Milla K, Getchell N, editors. Understanding the Cognitive Demands of the Purdue Pegboard Test: An fNIRs Study2021 2021. Cham: Springer International Publishing.

232. Chen S, Mao M, Zhu G, Chen Y, Qiu Y, Ye B, et al. Cortical activity in patients with high-functioning ischemic stroke during the Purdue Pegboard Test: insights into bimanual coordinated fine motor skills with functional near-infrared spectroscopy. Neural Regeneration Research. 2024;19(5).

233. Basu AP, Kirkpatrick EV, Wright B, Pearse JE, Best KE, Eyre JA. The Tyneside Pegboard Test: development, validation, and observations in unilateral cerebral palsy. Developmental medicine and child neurology. 2018;60(3):314-21.

234. Gogola GR, Velleman PF, Xu S, Morse AM, Lacy B, Aaron D. Hand dexterity in children: administration and normative values of the functional dexterity test. J Hand Surg Am. 2013;38(12):2426-31.

235. Tissue CM, Velleman PF, Stegink-Jansen CW, Aaron DH, Winthrop BG, Gogola GR. Validity and reliability of the Functional Dexterity Test in children. J Hand Ther. 2017;30(4):500-6.

236. Wagner LV, Davids JR. Assessment tools and classification systems used for the upper extremity in children with cerebral palsy. Clin Orthop Relat Res. 2012;470(5):1257-71.

237. Girard JM, Cohn JF. A Primer on Observational Measurement. Assessment. 2016;23(4):404-13.

238. Eken MM, Houdijk H, Doorenbosch CAM, Kiezebrink FEM, van Bennekom CAM, Harlaar J, et al. Relations between muscle endurance and subjectively reported fatigue, walking capacity, and participation in mildly affected adolescents with cerebral palsy. Developmental Medicine & Child Neurology. 2016;58(8):814-21.

239. Wrightson JG, Zewdie E, Kuo HC, Millet GY, Kirton A. Fatigue in children with perinatal stroke: clinical and neurophysiological associations. Developmental medicine and child neurology. 2020;62(2):234-40.

240. van Roon D, Steenbergen B, Meulenbroek RG. Trunk recruitment during spoon use in tetraparetic cerebral palsy. Exp Brain Res. 2004;155(2):186-95.

241. van Roon D, Steenbergen B, Meulenbroek RG. Trunk use and co-contraction in cerebral palsy as regulatory mechanisms for accuracy control. Neuropsychologia. 2005;43(4):497-508.

242. Hawe RL, Scott SH, Dukelow SP. Taking Proportional Out of Stroke Recovery. Stroke. 2019;50(1):204-11.

243. Saavedra SL, Goodworth AD. Postural Control in Children and Youth with Cerebral Palsy. In: Miller F, Bachrach S, Lennon N, O'Neil ME, editors. Cerebral Palsy. Cham: Springer International Publishing; 2020. p. 2565-86.

244. Scott SH, Dukelow SP. Potential of robots as next-generation technology for clinical assessment of neurological disorders and upper-limb therapy. J Rehabil Res Dev. 2011;48(4):335-53.

245. Neige C, Massé-Alarie H, Mercier C. Stimulating the Healthy Brain to Investigate Neural Correlates of Motor Preparation: A Systematic Review. Neural Plast. 2018;2018:5846096.

246. Cisek P, Kalaska JF. Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron. 2005;45(5):801-14.

247. Kravitz DJ, Saleem KS, Baker CI, Mishkin M. A new neural framework for visuospatial processing. Nat Rev Neurosci. 2011;12(4):217-30.

248. Battaglia-Mayer A, Caminiti R. Parieto-frontal networks for eye–hand coordination and movements. In: Vallar G, Coslett HB, editors. Handbook of Clinical Neurology. 151: Elsevier; 2018. p. 499-524.

249. Shmuelof L, Yang J, Caffo B, Mazzoni P, Krakauer JW. The neural correlates of learned motor acuity. J Neurophysiol. 2014;112(4):971-80.

250. Coderre AM, Zeid AA, Dukelow SP, Demmer MJ, Moore KD, Demers MJ, et al. Assessment of upper-limb sensorimotor function of subacute stroke patients using visually guided reaching. Neurorehabil Neural Repair. 2010;24(6):528-41.

251. Bosecker C, Dipietro L, Volpe B, Krebs HI. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. Neurorehabil Neural Repair. 2010;24(1):62-9.

252. Krebs HI, Krams M, Agrafiotis DK, DiBernardo A, Chavez JC, Littman GS, et al. Robotic measurement of arm movements after stroke establishes biomarkers of motor recovery. Stroke. 2014;45(1):200-4.

253. Wood MD, Simmatis LER, Jacobson JA, Dukelow SP, Boyd JG, Scott SH. Principal Components Analysis Using Data Collected From Healthy Individuals on Two Robotic Assessment Platforms Yields Similar Behavioral Patterns. Front Hum Neurosci. 2021;15:652201.

254. Wood MD, Simmatis LER, Gordon Boyd J, Scott SH, Jacobson JA. Using principal component analysis to reduce complex datasets produced by robotic technology in healthy participants. J Neuroeng Rehabil. 2018;15(1):71.

255. Wood M, Waterman A, Mon-Williams M, Hill L. Key kinematic measures of sensorimotor control identified via data reduction techniques in a population study (Born in Bradford). Wellcome Open Research. 2024;9(381).

256. Dobri SCD, Samdup D, Scott SH, Davies TC. Differentiating Motor Coordination and Position Sense in Children with Cerebral Palsy and Typically Developing Populations Through Robotic Assessments. Annu Int Conf IEEE Eng Med Biol Soc; Jul 102020. p. 3654-7.

257. Dobri SCD, Samdup D, Scott SH, Davies TC. Differentiating Motor Coordination in Children with Cerebral Palsy and Typically Developing Populations Through Exploratory Factor Analysis of Robotic Assessments. Annu Int Conf IEEE Eng Med Biol Soc. 2021;2021:5936-9.

258. Burn MB, Gogola GR. Dexterity of the Less Affected Hand in Children With Hemiplegic Cerebral Palsy. Hand (N Y). 2022;17(6):1114-21.

259. Zbytniewska-Megret M, Decraene L, Mailleux L, Kleeren L, Kanzler CM, Gassert R, et al. Reliable and Valid Robotic Assessments of Hand Active and Passive Position Sense in Children With Unilateral Cerebral Palsy. Front Hum Neurosci. 2022;16:895080.

260. Fooken J, Kreyenmeier P, Spering M. The role of eye movements in manual interception: A mini-review. Vision Res. 2021;183:81-90.

261. Goodale MA. Transforming vision into action. Vision Res. 2011;51(13):1567-87.

262. Goodale MA. Separate visual systems for perception and action: a framework for understanding cortical visual impairment. Developmental medicine and child neurology. 2013;55 Suppl 4:9-12.

263. Goodale MA. How (and why) the visual control of action differs from visual perception. Proc Biol Sci. 2014;281(1785):20140337.

264. Milner AD. How do the two visual streams interact with each other? Exp Brain Res. 2017;235(5):1297-308.

265. Marquez I, Trevino M. Visuomotor predictors of interception. PLoS One. 2024;19(9):e0308642.

266. Barany DA, Gomez-Granados A, Schrayer M, Cutts SA, Singh T. Perceptual decisions about object shape bias visuomotor coordination during rapid interception movements. J Neurophysiol. 2020;123(6):2235-48.

267. van Hof P, van der Kamp J, Savelsbergh GJ. The relation between infants' perception of catchableness and the control of catching. Dev Psychol. 2008;44(1):182-94.

268. von Hofsten C. Catching skills in infancy. J Exp Psychol Hum Percept Perform. 1983;9(1):75-85.

269. Nijhawan R. Visual prediction: psychophysics and neurophysiology of compensation for time delays. Behav Brain Sci. 2008;31(2):179-98; discussion 98-239.

270. Brenner E, Smeets JBJ. Continuously updating one's predictions underlies successful interception. J Neurophysiol. 2018;120(6):3257-74.

271. Fiehler K, Brenner E, Spering M. Prediction in goal-directed action. J Vis. 2019;19(9):10.

272. Fajen BR, Warren WH. Behavioral dynamics of intercepting a moving target. Exp Brain Res. 2007;180(2):303-19.

273. Chohan A, Savelsbergh GJ, van Kampen P, Wind M, Verheul MH. Postural adjustments and bearing angle use in interceptive actions. Exp Brain Res. 2006;171(1):47-55.

274. Chohan A, Verheul MH, Van Kampen PM, Wind M, Savelsbergh GJ. Children's use of the bearing angle in interceptive actions. J Mot Behav. 2008;40(1):18-28.

275. Brenner E, Smeets JB. Fast Responses of the Human Hand to Changes in Target Position. J Mot Behav. 1997;29(4):297-310.

276. Brenner E, Smeets JB, de Lussanet MH. Hitting moving targets. Continuous control of the acceleration of the hand on the basis of the target's velocity. Exp Brain Res. 1998;122(4):467-74.

277. Mazyn LI, Savelsbergh GJ, Montagne G, Lenoir M. Planning and on-line control of catching as a function of perceptual-motor constraints. Acta Psychol (Amst). 2007;126(1):59-78.

278. Zago M, McIntyre J, Senot P, Lacquaniti F. Visuo-motor coordination and internal models for object interception. Exp Brain Res. 2009;192(4):571-604.

279. Zhao H, Warren WH. On-line and model-based approaches to the visual control of action. Vision Res. 2015;110(Pt B):190-202.

280. Von Hofsten C. Action, the foundation for cognitive development. Scand J Psychol. 2009;50(6):617-23.

281. Newell KM. Constraints on the development of coordination. In: Wade MG, Whiting HTA, editors. Motor development on children: Aspects of coordination and control. Dordrecht: Martinus Nijhoff Publishers; 1986. p. 341-60.

282. Ricken AX, Savelsbergh GJ, Bennett SJ. External timing constraints facilitate performance of everyday interceptive actions in children with Spastic Hemiparetic Cerebral Palsy. Neurosci Lett. 2006;410(3):187-92.

283. Ricken AX, Bennett SJ, Savelsbergh GJ. Coordination of reaching in children with spastic hemiparetic cerebral palsy under different task demands. Motor Control. 2005;9(4):357-71.

284. Ricken AX, Savelsbergh GJ, Bennett SJ. Interception of moving objects while walking in children with spastic hemiparetic cerebral palsy. Disabil Rehabil. 2007;29(1):69-77.

285. van Kampen PM, Ledebt A, Savelsbergh GJ. Visual guidance during an interception task in children with Spastic Hemiparetic Cerebral Palsy. Neurosci Lett. 2008;432(1):7-12.

286. van Kampen PM, Ledebt A, Deconinck FJ, Savelsbergh GJ. Visual guidance of interceptive actions in children with spastic unilateral cerebral palsy is influenced by the side of the lesion. Disabil Rehabil. 2010;32(18):1527-37.

287. van Kampen PM, Ledebt A, Smorenburg AR, Vermeulen RJ, Kelder ME, van der Kamp J, et al. Gaze behaviour during interception in children with spastic unilateral cerebral palsy. Res Dev Disabil. 2012;33(1):45-53.

288. Johnson-Frey SH, Newman-Norlund R, Grafton ST. A distributed left hemisphere network active during planning of everyday tool use skills. Cereb Cortex. 2005;15(6):681-95.

289. van Thiel E, Meulenbroek RG, Hulstijn W, Steenbergen B. Kinematics of fast hemiparetic aiming movements toward stationary and moving targets. Exp Brain Res. 2000;132(2):230-42.

290. Passingham RE, Wise SP. The neurobiology of the prefrontal cortex : anatomy, evolution, and the origin of insight. 1st ed. Oxford: Oxford Univ. Press; 2012.

291. Passingham RE, Lau H. Do we understand the prefrontal cortex? Brain Struct Funct. 2023;228(5):1095-105.

292. Fuster JM. The prefrontal cortex. Fifth edition. ed. Amsterdam ;: Elsevier/Academic Press; 2015.

293. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology. 2022;47(1):72-89.

294. Fuster JM. The prefrontal cortex - An update: time is of the essence. Neuron. 2001;30(2):319-33.

295. Fine JM, Hayden BY. The whole prefrontal cortex is premotor cortex. Philos Trans R Soc Lond B Biol Sci. 2022;377(1844):20200524.

296. Badre D, Nee DE. Frontal Cortex and the Hierarchical Control of Behavior. Trends Cogn Sci. 2018;22(2):170-88.

297. Fuster JM. The cognit: a network model of cortical representation. Int J Psychophysiol. 2006;60(2):125-32.

298. Alonso R, Brocas I, Carrillo JD. Resource Allocation in the Brain. The Review of Economic Studies. 2013;81(2):501-34.

299. Baghdassarian HM, Lewis NE. Resource allocation in mammalian systems. Biotechnol Adv. 2024;71:108305.

300. Sakai K. Task set and prefrontal cortex. Annu Rev Neurosci. 2008;31(1):219-45.

301. Basso JC, Shang A, Elman M, Karmouta R, Suzuki WA. Acute Exercise Improves Prefrontal Cortex but not Hippocampal Function in Healthy Adults. J Int Neuropsychol Soc. 2015;21(10):791-801.

302. Bigliassi M, Filho E. Functional significance of the dorsolateral prefrontal cortex during exhaustive exercise. Biol Psychol. 2022;175:108442.

303. Dietrich A. Transient hypofrontality as a mechanism for the psychological effects of exercise. Psychiatry Res. 2006;145(1):79-83.

304. Jung M, Ryu S, Kang M, Javadi AH, Loprinzi PD. Evaluation of the transient hypofrontality theory in the context of exercise: A systematic review with meta-analysis. Q J Exp Psychol (Hove). 2022;75(7):1193-214.

305. Sato JR, Gianlorenço AC, Fernandes EB, da Rocha TF, Makiyama AM, Dipietro L. An Experiment Using Functional Near-Infrared Spectroscopy and Robot-Assisted Multi-Joint Pointing Movements of the Lower Limb. J Vis Exp. 2024(208):19.

306. Kim HY, Yang SP, Park GL, Kim EJ, You JS. Best facilitated cortical activation during different stepping, treadmill, and robot-assisted walking training paradigms and speeds: A functional near-infrared spectroscopy neuroimaging study. NeuroRehabilitation. 2016;38(2):171-8.

307. Robinson MN, Peake LJ, Ditchfield MR, Reid SM, Lanigan A, Reddihough DS. Magnetic resonance imaging findings in a population-based cohort of children with cerebral palsy. Developmental medicine and child neurology. 2009;51(1):39-45.

308. de Vries LS, van Haastert IC, Benders MJ, Groenendaal F. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med. 2011;16(5):279-87.

309. Laporta-Hoyos O, Pannek K, Pagnozzi AM, Whittingham K, Wotherspoon J, Benfer K, et al. Cognitive, academic, executive and psychological functioning in children with spastic motor type cerebral palsy: Influence of extent, location, and laterality of brain lesions. Eur J Paediatr Neurol. 2022;38:33-46.

310. Forssberg H, Eliasson AC, Redon-Zouitenn C, Mercuri E, Dubowitz L. Impaired grip-lift synergy in children with unilateral brain lesions. Brain. 1999;122 (Pt 6):1157-68.

311. Mailleux L, Simon-Martinez C, Klingels K, Jaspers E, Desloovere K, Demaerel P, et al. Structural Brain Damage and Upper Limb Kinematics in Children with Unilateral Cerebral Palsy. Front Hum Neurosci. 2017;11:607.

312. Klingels K, Jaspers E, Staudt M, Guzzetta A, Mailleux L, Ortibus E, et al. Do mirror movements relate to hand function and timing of the brain lesion in children with unilateral cerebral palsy? Developmental medicine and child neurology. 2016;58(7):735-42.

313. Reid LB, Rose SE, Boyd RN. Rehabilitation and neuroplasticity in children with unilateral cerebral palsy. Nat Rev Neurol. 2015;11(7):390-400.

314. Lewis SA, Ruttenberg A, Iyiyol T, Kong N, Jin SC, Kruer MC. Potential clinical applications of advanced genomic analysis in cerebral palsy. EBioMedicine. 2024;106:105229.

315. Romero B, Robinson KG, Batish M, Akins RE. An Emerging Role for Epigenetics in Cerebral Palsy. J Pers Med. 2021;11(11).

316. Islam M, Nordstrand L, Holmstrom L, Kits A, Forssberg H, Eliasson AC. Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? Developmental medicine and child neurology. 2014;56(3):252-8.

317. Damiano DL, Pekar JJ, Mori S, Faria AV, Ye X, Stashinko E, et al. Functional and Structural Brain Connectivity in Children With Bilateral Cerebral Palsy Compared to Age-Related Controls and in Response to Intensive Rapid-Reciprocal Leg Training. Front Rehabil Sci. 2022;3:811509.

318. Brown GG, Perthen JE, Liu TT, Buxton RB. A primer on functional magnetic resonance imaging. Neuropsychol Rev. 2007;17(2):107-25.

319. Phillips JP, Sullivan KJ, Burtner PA, Caprihan A, Provost B, Bernitsky-Beddingfield A. Ankle dorsiflexion fMRI in children with cerebral palsy undergoing intensive body-weight-supported treadmill training: a pilot study. Developmental medicine and child neurology. 2007;49(1):39-44.

320. Doucet GE, Baker S, Wilson TW, Kurz MJ. Weaker Connectivity of the Cortical Networks Is Linked with the Uncharacteristic Gait in Youth with Cerebral Palsy. Brain Sci. 2021;11(8).

321. Inguaggiato E, Sgandurra G, Perazza S, Guzzetta A, Cioni G. Brain reorganization following intervention in children with congenital hemiplegia: a systematic review. Neural Plast. 2013;2013:356275.

322. Manning KY, Fehlings D, Mesterman R, Gorter JW, Switzer L, Campbell C, et al. Resting State and Diffusion Neuroimaging Predictors of Clinical Improvements Following Constraint-Induced Movement Therapy in Children With Hemiplegic Cerebral Palsy. J Child Neurol. 2015;30(11):1507-14.

323. Ilves N, Ilves P, Laugesaar R, Juurmaa J, Mannamaa M, Loo S, et al. Resting-State Functional Connectivity and Cognitive Impairment in Children with Perinatal Stroke. Neural Plast. 2016;2016:2306406.

324. Carlson HL, Sugden C, Brooks BL, Kirton A. Functional connectivity of language networks after perinatal stroke. Neuroimage Clin. 2019;23:101861.

325. Greene DJ, Koller JM, Hampton JM, Wesevich V, Van AN, Nguyen AL, et al. Behavioral interventions for reducing head motion during MRI scans in children. Neuroimage. 2018;171:234-45.

326. Parkes L, Fulcher B, Yucel M, Fornito A. An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. Neuroimage. 2018;171:415-36.

327. Stadskleiv K, Jahnsen R, Andersen GL, von Tetzchner S. Neuropsychological profiles of children with cerebral palsy. Developmental Neurorehabilitation. 2018;21(2):108-20.

328. Patil AV, Safaie J, Moghaddam HA, Wallois F, Grebe R. Experimental investigation of NIRS spatial sensitivity. Biomed Opt Express. 2011;2(6):1478-93.

329. Schmit JM, Riley M, Cummins-Sebree S, Schmitt L, Shockley K. Functional Task Constraints Foster Enhanced Postural Control in Children With Cerebral Palsy. Phys Ther. 2016;96(3):348-54.

330. Okamoto M, Dan H, Shimizu K, Takeo K, Amita T, Oda I, et al. Multimodal assessment of cortical activation during apple peeling by NIRS and fMRI. Neuroimage. 2004;21(4):1275-88.

331. Kirilina E, Jelzow A, Heine A, Niessing M, Wabnitz H, Bruhl R, et al. The physiological origin of task-evoked systemic artefacts in functional near infrared spectroscopy. Neuroimage. 2012;61(1):70-81.

332. Doherty EJ, Spencer CA, Burnison J, Ceko M, Chin J, Eloy L, et al. Interdisciplinary views of fNIRS: Current advancements, equity challenges, and an agenda for future needs of a diverse fNIRS research community. Front Integr Neurosci. 2023;17:1059679.

333. Khan B, Wildey C, Francis R, Tian F, Delgado MR, Liu H, et al. Improving optical contact for functional near-infrared brain spectroscopy and imaging with brush optodes. Biomed Opt Express. 2012;3(5):878-98.

334. Giacometti P, Diamond SG. Compliant head probe for positioning electroencephalography electrodes and near-infrared spectroscopy optodes. J Biomed Opt. 2013;18(2):27005.

335. Mailleux L, Franki I, Emsell L, Peedima ML, Fehrenbach A, Feys H, et al. The relationship between neuroimaging and motor outcome in children with cerebral palsy: A systematic review-Part B diffusion imaging and tractography. Res Dev Disabil. 2020;97:103569.

336. Franki I, Mailleux L, Emsell L, Peedima ML, Fehrenbach A, Feys H, et al. The relationship between neuroimaging and motor outcome in children with cerebral palsy: A systematic review - Part A. Structural imaging. Res Dev Disabil. 2020;100:103606.

337. Su WC, Colacot R, Ahmed N, Nguyen T, George T, Gandjbakhche A. The use of functional near-infrared spectroscopy in tracking neurodevelopmental trajectories in infants and children with or without developmental disorders: a systematic review. Front Psychiatry. 2023;14:1210000.

338. Monden Y, Dan I, Nagashima M, Dan H, Uga M, Ikeda T, et al. Individual classification of ADHD children by right prefrontal hemodynamic responses during a go/no-go task as assessed by fNIRS. Neuroimage Clin. 2015;9:1-12.

339. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018;18(1):143.

340. Lockwood C, Dos Santos KB, Pap R. Practical Guidance for Knowledge Synthesis: Scoping Review Methods. Asian Nurs Res (Korean Soc Nurs Sci). 2019;13(5):287-94.

341. Khalil H, Peters M, Godfrey CM, McInerney P, Soares CB, Parker D. An Evidence-Based Approach to Scoping Reviews. Worldviews Evid Based Nurs. 2016;13(2):118-23.

342. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-73.

343. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Implement. 2021;19(1):3-10.

344. Penfold R. Using the Lens Database for Staff Publications. Journal of the Medical Library Association. 2020;108(2):341-4.

345. Miles M, Rodrigues A, Tajali S, Xiong Y, Orchanian-Cheff A, Reid WD, et al. Muscle and cerebral oxygenation during cycling in chronic obstructive pulmonary disease: A scoping review. Chron Respir Dis. 2021;18:1479973121993494.

346. Gentles S, Duku E, Kerns C, McVey AJ, Hunsche MC, Ng Cordell EC, et al. Trajectory research in children on the autism spectrum: a scoping review protocol. BMJ Open. 2021;11(11):e053443.

347. Le Cunff AL, Dommett E, Giampietro V. Neurophysiological measures and correlates of cognitive load in attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and dyslexia: A scoping review and research recommendations. Eur J Neurosci. 2024;59(2):256-82.

348. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

349. Parazzini C, Baldoli C, Scotti G, Triulzi F. Terminal zones of myelination: MR evaluation of children aged 20-40 months. AJNR Am J Neuroradiol. 2002;23(10):1669-73.

350. Irving DB, Cook JL, Menz HB. Factors associated with chronic plantar heel pain: a systematic review. J Sci Med Sport. 2006;9(1-2):11-22; discussion 3-4.

351. Zhang T, Xu G, Huo C, Li W, Li Z, Li W. Cortical hemodynamic response and networks in children with cerebral palsy during upper limb bilateral motor training. J Biophotonics. 2023;16(5):e202200326.

352. Chaudhary U, Hall M, Gonzalez J, Elbaum L, Bloyer M, Godavarty A. Motor response investigation in individuals with cerebral palsy using near infrared spectroscopy: pilot study. Appl Opt. 2014;53(3):503-10.

353. Xie P, Nie Z, Zhang T, Xu G, Sun A, Chen T, et al. FNIRS based study of brain network characteristics in children with cerebral palsy during bilateral lower limb movement. Med Phys. 2024;51(6):4434-46.

354. Olusanya BO, Gladstone M, Wright SM, Hadders-Algra M, Boo NY, Nair MKC, et al. Cerebral palsy and developmental intellectual disability in children younger than

5 years: Findings from the GBD-WHO Rehabilitation Database 2019. Front Public Health. 2022;10:894546.

355. Di Lonardo Burr SM, Pirazzoli L, Dopierala AW, Bejjanki VR, Nelson CA, Emberson LL. Longitudinal assessments of functional near-infrared spectroscopy background functional connectivity in low- and middle-income infants during a social cognition task. J Exp Psychol Gen. 2024;153(3):798-813.

356. Lloyd-Fox S, McCann S, Milosavljevic B, Katus L, Blasi A, Bulgarelli C, et al. The Brain Imaging for Global Health (BRIGHT) Project: Longitudinal cohort study protocol. Gates Open Research. 2023;7(126).

357. Ballester-Plane J, Schmidt R, Laporta-Hoyos O, Junque C, Vazquez E, Delgado I, et al. Whole-brain structural connectivity in dyskinetic cerebral palsy and its association with motor and cognitive function. Hum Brain Mapp. 2017;38(9):4594-612.

358. Qin Y, Li Y, Sun B, He H, Peng R, Zhang T, et al. Functional Connectivity Alterations in Children with Spastic and Dyskinetic Cerebral Palsy. Neural Plast. 2018;2018:7058953.

359. Schroeder PA, Artemenko C, Kosie JE, Cockx H, Stute K, Pereira J, et al. Using preregistration as a tool for transparent fNIRS study design. Neurophoton. 2023;10(2):023515.

360. Reid LB, Pagnozzi AM, Fiori S, Boyd RN, Dowson N, Rose SE. Measuring neuroplasticity associated with cerebral palsy rehabilitation: An MRI based power analysis. Int J Dev Neurosci. 2017;58:17-25.

361. Frank MC, Bergelson E, Bergmann C, Cristia A, Floccia C, Gervain J, et al. A Collaborative Approach to Infant Research: Promoting Reproducibility, Best Practices, and Theory-Building. Infancy. 2017;22(4):421-35.

362. Pinti P, Scholkmann F, Hamilton A, Burgess P, Tachtsidis I. Current Status and Issues Regarding Pre-processing of fNIRS Neuroimaging Data: An Investigation of Diverse Signal Filtering Methods Within a General Linear Model Framework. Front Hum Neurosci. 2018;12:505.

363. Gervain J. ManyBabies3NIRS: a large-scale, multi-lab NIRS replication study assessing infants' ability to extract regularities from speech 2022 [Available from: https://manybabies.org/MB3N/.

364. Reid SM, Carlin JB, Reddihough DS. Using the Gross Motor Function Classification System to describe patterns of motor severity in cerebral palsy. Developmental medicine and child neurology. 2011;53(11):1007-12.

365. Bailes AF, Greve K, Long J, Kurowski BG, Vargus-Adams J, Aronow B, et al. Describing the Delivery of Evidence-Based Physical Therapy Intervention to Individuals With Cerebral Palsy. Pediatr Phys Ther. 2021;33(2):65-72.

366. Van de Winckel A, Klingels K, Bruyninckx F, Wenderoth N, Peeters R, Sunaert S, et al. How does brain activation differ in children with unilateral cerebral palsy compared to typically developing children, during active and passive movements, and tactile stimulation? An fMRI study. Res Dev Disabil. 2013;34(1):183-97.

367. Novak I, Morgan C, Fahey M, Finch-Edmondson M, Galea C, Hines A, et al. State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy. Curr Neurol Neurosci Rep. 2020;20(2):3.

368. Kuo HC, Friel KM, Gordon AM. Neurophysiological mechanisms and functional impact of mirror movements in children with unilateral spastic cerebral palsy. Developmental medicine and child neurology. 2018;60(2):155-61.

369. Norton J, Sawicka K. The significance of hand movement mirroring in cerebral palsy. Developmental medicine and child neurology. 2016;58(7):655-6.

370. Simon-Martinez C, Decraene L, Zielinski I, Hoare B, Williams J, Mailleux L, et al. The impact of brain lesion characteristics and the corticospinal tract wiring on mirror movements in unilateral cerebral palsy. Sci Rep. 2022;12(1):16301.

371. Zielinski IM, Steenbergen B, Schmidt A, Klingels K, Simon Martinez C, de Water P, et al. Windmill-task as a New Quantitative and Objective Assessment for Mirror Movements in Unilateral Cerebral Palsy: A Pilot Study. Arch Phys Med Rehabil. 2018;99(8):1547-52.

372. Ward NS. Functional reorganization of the cerebral motor system after stroke. Curr Opin Neurol. 2004;17(6):725-30.

373. Araneda R, Dricot L, Ebner-Karestinos D, Paradis J, Gordon AM, Friel KM, et al. Brain activation changes following motor training in children with unilateral cerebral palsy: An fMRI study. Ann Phys Rehabil Med. 2021;64(3):101502.

374. Hilderley AJ, Taylor MJ, Fehlings D, Chen JL, Wright FV. Optimization of fMRI methods to determine laterality of cortical activation during ankle movements of children with unilateral cerebral palsy. Int J Dev Neurosci. 2018;66:54-62.

375. Hinchberger V, Kang SH, Kline J, Stanley CJ, Bulea TC, Damiano DL. Investigation of brain mechanisms underlying upper limb function in bilateral cerebral palsy using EEG. Clin Neurophysiol. 2023;151:116-27.

376. Phillips C, Kline J, Stanley CJ, Bulea TC, Damiano DL. Children With Bilateral Cerebral Palsy Exhibit Bimanual Asymmetric Motor Deficits and EEG Evidence of

Dominant Sensorimotor Hemisphere Overreliance During Reaching. Neurorehabil Neural Repair. 2023;37(9):617-27.

377. Himmelmann K, Horber V, Sellier E, De la Cruz J, Papavasiliou A, Krageloh-Mann I, et al. Neuroimaging Patterns and Function in Cerebral Palsy-Application of an MRI Classification. Front Neurol. 2020;11:617740.

378. Hilderley AJ, Wright FV, Taylor MJ, Chen JL, Fehlings D. Functional Neuroplasticity and Motor Skill Change Following Gross Motor Interventions for Children With Diplegic Cerebral Palsy. Neurorehabil Neural Repair. 2023;37(1):16-26.

379. Orihuela-Espina F, Leff DR, James DR, Darzi AW, Yang GZ. Quality control and assurance in functional near infrared spectroscopy (fNIRS) experimentation. Phys Med Biol. 2010;55(13):3701-24.

380. Goodale MA. Transforming abstract plans into concrete actions. Proceedings of the National Academy of Sciences. 2020;117(47):29265-7.

381. Zimonyi N, Koi T, Dombradi V, Imrei M, Nagy R, Pulay MA, et al. Comparison of Executive Function Skills between Patients with Cerebral Palsy and Typically Developing Populations: A Systematic Review and Meta-Analysis. JCM. 2024;13(7).

382. Oudgenoeg-Paz O, Mulder H, Jongmans MJ, van der Ham IJM, Van der Stigchel S. The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. Neuroscience & Biobehavioral Reviews. 2017;80:382-93.

383. Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Dev. 2000;71(1):44-56.

384. Piitulainen H, Kulmala JP, Maenpaa H, Rantalainen T. The gait is less stable in children with cerebral palsy in normal and dual-task gait compared to typically developed peers. J Biomech. 2021;117:110244.

385. Roostaei M, Raji P, Morone G, Razi B, Khademi-Kalantari K. The effect of dual-task conditions on gait and balance performance in children with cerebral palsy: A systematic review and meta-analysis of observational studies. J Bodyw Mov Ther. 2021;26:448-62.

386. Trevarrow MP, Reelfs A, Ott LR, Penhale SH, Lew BJ, Goeller J, et al. Altered spontaneous cortical activity predicts pain perception in individuals with cerebral palsy. Brain Commun. 2022;4(2):fcac087.

387. Herold F, Wiegel P, Scholkmann F, Muller NG. Applications of Functional Near-Infrared Spectroscopy (fNIRS) Neuroimaging in Exercise(-)Cognition Science: A Systematic, Methodology-Focused Review. JCM. 2018;7(12).

388. Simon-Martinez C, Jaspers E, Alaerts K, Ortibus E, Balsters J, Mailleux L, et al. Influence of the corticospinal tract wiring pattern on sensorimotor functional connectivity and clinical correlates of upper limb function in unilateral cerebral palsy. Sci Rep. 2019;9(1):8230.

389. Duan SF, Mu XT, Huang Q, Ma Y, Shan BC. Occult Spastic Diplegic Cerebral Palsy Recognition Using Efficient Machine Learning for Big Data and Structural Connectivity Abnormalities Analysis. Journal of Medical Imaging and Health Informatics. 2018;8(2):317-24.

390. Zhang W, Zhang S, Zhu M, Tang J, Zhao X, Wang Y, et al. Changes of Structural Brain Network Following Repetitive Transcranial Magnetic Stimulation in Children With Bilateral Spastic Cerebral Palsy: A Diffusion Tensor Imaging Study. Front Pediatr. 2020;8:617548.

391. Burton H, Dixit S, Litkowski P, Wingert JR. Functional connectivity for somatosensory and motor cortex in spastic diplegia. Somatosens Mot Res. 2009;26(4):90-104.

392. Mu X, Wang Z, Nie B, Duan S, Ma Q, Dai G, et al. Altered regional and circuit resting-state activity in patients with occult spastic diplegic cerebral palsy. Pediatr Neonatol. 2018;59(4):345-51.

393. Bauer CM, Papadelis C. Alterations in the Structural and Functional Connectivity of the Visuomotor Network of Children With Periventricular Leukomalacia. Semin Pediatr Neurol. 2019;31:48-56.

394. Vidal-Rosas EE, von Luhmann A, Pinti P, Cooper RJ. Wearable, high-density fNIRS and diffuse optical tomography technologies: a perspective. Neurophoton. 2023;10(2):023513.

395. Hocke LM, Oni IK, Duszynski CC, Corrigan AV, Frederick BD, Dunn JF. Automated Processing of fNIRS Data-A Visual Guide to the Pitfalls and Consequences. Algorithms. 2018;11(5).

396. Hernandez SM, Pollonini L, editors. NIRSplot: A Tool for Quality Assessment of fNIRS Scans. Biophotonics Congress: Biomedical Optics 2020 (Translational, Microscopy, OCT, OTS, BRAIN); 2020 2020/04/20; Washington, DC: Optical Society of America.

397. Sappia MS, Hakimi N, Colier W, Horschig JM. Signal quality index: an algorithm for quantitative assessment of functional near infrared spectroscopy signal quality. Biomed Opt Express. 2020;11(11):6732-54.

398. Klein F, Kranczioch C. Signal Processing in fNIRS: A Case for the Removal of Systemic Activity for Single Trial Data. Front Hum Neurosci. 2019;13:331.

399. Klein F, Lührs M, Benitez-Andonegui A, Roehn P, Kranczioch C. Performance comparison of systemic activity correction in functional near-infrared spectroscopy for methods with and without short distance channels. Neurophoton. 2022;10(1):013503.

400. Tak S, Ye JC. Statistical analysis of fNIRS data: a comprehensive review. Neuroimage. 2014;85 Pt 1:72-91.

401. Santosa H, Aarabi A, Perlman SB, Huppert TJ. Characterization and correction of the false-discovery rates in resting state connectivity using functional near-infrared spectroscopy. J Biomed Opt. 2017;22(5):55002.

402. Yücel MA, Lühmann Av, Scholkmann F, Gervain J, Dan I, Ayaz H, et al. Best practices for fNIRS publications. Neurophoton. 2021;8(1):012101.

403. McCall JV, Ludovice MC, Elliott C, Kamper DG. Hand function development of children with hemiplegic cerebral palsy: A scoping review. J Pediatr Rehabil Med. 2022;15(1):211-28.

404. De Campos AC, Hidalgo-Robles A, Longo E, Shrader C, Paleg G. F-words and early intervention ingredients for non-ambulant children with cerebral palsy: A scoping review. Developmental medicine and child neurology. 2024;66(1):41-51.

405. Bell AH, Miller SL, Castillo-Melendez M, Malhotra A. The Neurovascular Unit: Effects of Brain Insults During the Perinatal Period. Front Neurosci. 2019;13:1452.

406. Pinti P, Tachtsidis I, Hamilton A, Hirsch J, Aichelburg C, Gilbert S, et al. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Ann N Y Acad Sci. 2020;1464(1):5-29.

407. Paranawithana I, Mao D, Wong YT, McKay CM. Reducing false discoveries in resting-state functional connectivity using short channel correction: an fNIRS study. Neurophoton. 2022;9(1):015001.

408. Zhao H, Frijia EM, Vidal Rosas E, Collins-Jones L, Smith G, Nixon-Hill R, et al. Design and validation of a mechanically flexible and ultra-lightweight high-density diffuse optical tomography system for functional neuroimaging of newborns. Neurophoton. 2021;8(1):015011.

409. Pfeifer MD, Scholkmann F, Labruyere R. Signal Processing in Functional Near-Infrared Spectroscopy (fNIRS): Methodological Differences Lead to Different Statistical Results. Front Hum Neurosci. 2017;11:641.

410. Sato JR, Junior CEB, de Araujo ELM, de Souza Rodrigues J, Andrade SM. A guide for the use of fNIRS in microcephaly associated to congenital Zika virus infection. Sci Rep. 2021;11(1):19270.

411. Mihara M, Miyai I. Review of functional near-infrared spectroscopy in neurorehabilitation. Neurophoton. 2016;3(3):031414.

412. Gallagher A, Wallois F, Obrig H. Functional near-infrared spectroscopy in pediatric clinical research: Different pathophysiologies and promising clinical applications. Neurophoton. 2023;10(2):023517.

413. Nishiyori R. fNIRS: An Emergent Method to Document Functional Cortical Activity during Infant Movements. Front Psychol. 2016;7:533.

414. Cacola P, Getchell N, Srinivasan D, Alexandrakis G, Liu H. Cortical activity in fine-motor tasks in children with Developmental Coordination Disorder: A preliminary fNIRS study. Int J Dev Neurosci. 2018;65:83-90.

415. Biallas M, Trajkovic I, Hagmann C, Scholkmann F, Jenny C, Holper L, et al. Multimodal recording of brain activity in term newborns during photic stimulation by near-infrared spectroscopy and electroencephalography. J Biomed Opt. 2012;17(8):086011-1.

416. Scarapicchia V, Brown C, Mayo C, Gawryluk JR. Functional Magnetic Resonance Imaging and Functional Near-Infrared Spectroscopy: Insights from Combined Recording Studies. Front Hum Neurosci. 2017;11:419.

417. Li R, Yang D, Fang F, Hong KS, Reiss AL, Zhang Y. Concurrent fNIRS and EEG for Brain Function Investigation: A Systematic, Methodology-Focused Review. Sensors (Basel). 2022;22(15).

418. Ru X, He K, Lyu B, Li D, Xu W, Gu W, et al. Multimodal neuroimaging with optically pumped magnetometers: A simultaneous MEG-EEG-fNIRS acquisition system. Neuroimage. 2022;259:119420.

419. Grassler B, Herold F, Dordevic M, Gujar TA, Darius S, Bockelmann I, et al. Multimodal measurement approach to identify individuals with mild cognitive impairment: study protocol for a cross-sectional trial. BMJ Open. 2021;11(5):e046879.

420. Chen S, Zhang X, Chen X, Zhou Z, Cong W, Chong K, et al. The assessment of interhemispheric imbalance using functional near-infrared spectroscopic and transcranial magnetic stimulation for predicting motor outcome after stroke. Front Neurosci. 2023;17:1231693.

421. Curtin A, Tong S, Sun J, Wang J, Onaral B, Ayaz H. A Systematic Review of Integrated Functional Near-Infrared Spectroscopy (fNIRS) and Transcranial Magnetic Stimulation (TMS) Studies. Front Neurosci. 2019;13:84.

422. Berger A, Horst F, Muller S, Steinberg F, Doppelmayr M. Current State and Future Prospects of EEG and fNIRS in Robot-Assisted Gait Rehabilitation: A Brief Review. Front Hum Neurosci. 2019;13:172.

423. Scholkmann F, Holper L, Wolf U, Wolf M. A new methodical approach in neuroscience: assessing inter-personal brain coupling using functional near-infrared imaging (fNIRI) hyperscanning. Front Hum Neurosci. 2013;7:813.

424. Jadavji Z, Kirton A, Metzler MJ, Zewdie E. BCI-activated electrical stimulation in children with perinatal stroke and hemiparesis: A pilot study. Front Hum Neurosci. 2023;17:1006242.

425. Asanani N. Study of NIRS based motor cortex activation patterns in cerebral palsy affected kids using image based metrics [Thesis]: The University of Texas at Arlington; 2008.

426. Parlapalli R. Comparison of hemodynamic response non-linearity using simultaneous near infrared spectroscopy and magnetic resonance imaging modalities [Thesis]: The University of Texas at Arlington; 2008.

427. Dhamne SC. Diffuse optical imaging of brain function under repetitive transcranial magnetic stimulation and in children with cerebral palsy [Dissertation]: The University of Texas at Arlington; 2009.

428. Khan B. Functional near infrared spectroscopy for the assessment of motor cortex plasticity in pediatric subjects affected by cerebral palsy [Dissertation]: The University of Texas at Arlington; 2009.

429. MacGregor R. Effects of specifically sequenced massage on spastic muscle properties and motor skills in adolescents with cerebral palsy. 2009.

430. Chaudhary U. Functional near infrared spectroscopy study of language, joint attention and motor skills [Thesis]: Florida International University; 2013.

431. Hervey N. A GLM/ICA analysis using motion tracking and electromyography differentiates between brain activation due to intended and unintended motions in fNIRS images acquired during a finger tapping task performed by children with cerebral palsy [Dissertation]: The University of Texas at Arlington; 2014.

432. Surkar SM. Identification and Intervention for Action Planning Deficits in Children With Hemiplegic Cerebral Palsy [Dissertation]: University of Nebraska; 2016.

433. Cao J. Revealing Hemodynamic Response and Dynamic Changes in Functional Cortical Networks Using Functional Near-Infrared Spectroscopy (FNIRS) [Dissertation]: The University of Texas at Arlington; 2017.

434. Licea J. Interrelationships among brain, muscle and physical activity in children with cerebral palsy [Dissertation]: University of Georgia; 2023.

435. Raggam P, Bauernfeind G, Wriessnegger SC. NICA: A Novel Toolbox for Near-Infrared Spectroscopy Calculations and Analyses. Front Neuroinform. 2020;14:26.

436. Huppert TJ, Diamond SG, Franceschini MA, Boas DA. HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt. 2009;48(10):D280-98.

437. Huppert TJ. Commentary on the statistical properties of noise and its implication on general linear models in functional near-infrared spectroscopy. Neurophoton. 2016;3(1):010401.

438. Santosa H, Zhai X, Fishburn F, Huppert T. The NIRS Brain AnalyzIR Toolbox. Algorithms. 2018;11(5):73.

439. Barker JW, Aarabi A, Huppert TJ. Autoregressive model based algorithm for correcting motion and serially correlated errors in fNIRS. Biomed Opt Express. 2013;4(8):1366-79.

440. Fishburn FA, Ludlum RS, Vaidya CJ, Medvedev AV. Temporal Derivative Distribution Repair (TDDR): A motion correction method for fNIRS. Neuroimage. 2019;184:171-9.

441. Jahani S, Setarehdan SK, Boas DA, Yucel MA. Motion artifact detection and correction in functional near-infrared spectroscopy: a new hybrid method based on spline interpolation method and Savitzky-Golay filtering. Neurophoton. 2018;5(1):015003.

442. Bauernfeind G, Wriessnegger SC, Daly I, Muller-Putz GR. Separating heart and brain: on the reduction of physiological noise from multichannel functional near-infrared spectroscopy (fNIRS) signals. J Neural Eng. 2014;11(5):056010.

443. Quaresima V, Ferrari M. A Mini-Review on Functional Near-Infrared Spectroscopy (fNIRS): Where Do We Stand, and Where Should We Go? Photonics. 2019;6(3):87.

444. Delgado Reyes LM, Bohache K, Wijeakumar S, Spencer JP. Evaluating motion processing algorithms for use with functional near-infrared spectroscopy data from young children. Neurophoton. 2018;5(2):025008.

445. Gagnon L, Cooper RJ, Yucel MA, Perdue KL, Greve DN, Boas DA. Short separation channel location impacts the performance of short channel regression in NIRS. Neuroimage. 2012;59(3):2518-28.

446. Kinder KT, Heim HLR, Parker J, Lowery K, McCraw A, Eddings RN, et al. Systematic review of fNIRS studies reveals inconsistent chromophore data reporting practices. Neurophoton. 2022;9(4):040601.

447. Cui X, Bray S, Reiss AL. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. Neuroimage. 2010;49(4):3039-46.

448. Zimeo Morais GA, Scholkmann F, Balardin JB, Furucho RA, de Paula RCV, Biazoli CE, Jr., et al. Non-neuronal evoked and spontaneous hemodynamic changes in the anterior temporal region of the human head may lead to misinterpretations of functional near-infrared spectroscopy signals. Neurophoton. 2018;5(1):011002.

449. Lloyd-Fox S, Blasi A, Elwell CE. Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. Neuroscience & Biobehavioral Reviews. 2010;34(3):269-84.

450. Sakatani K, Murata Y, Fujiwara N, Hoshino T, Nakamura S, Kano T, et al. Comparison of blood-oxygen-level-dependent functional magnetic resonance imaging and near-infrared spectroscopy recording during functional brain activation in patients with stroke and brain tumors. J Biomed Opt. 2007;12(6):062110.

451. Yamada T, Umeyama S, Matsuda K. Separation of fNIRS signals into functional and systemic components based on differences in hemodynamic modalities. PLoS One. 2012;7(11):e50271.

452. Tian F, Sepulveda P, Kota S, Liu Y, Das Y, Liu H, et al. Regional heterogeneity of cerebral hemodynamics in mild neonatal encephalopathy measured with multichannel near-infrared spectroscopy. Pediatr Res. 2021;89(4):882-8.

453. Harbourne R, Kamm K. Upper extremity function: What's posture got to do with it? J Hand Ther. 2015;28(2):106-12; quiz 13.

454. Lemmens RJ, Janssen-Potten YJ, Timmermans AA, Defesche A, Smeets RJ, Seelen HA. Arm hand skilled performance in cerebral palsy: activity preferences and their movement components. BMC Neurol. 2014;14:52.

455. Dan B, Rosenbaum P, Carr L, Gough M, Coughlan J, Nweke N. Proposed updated description of cerebral palsy. Developmental medicine and child neurology. 2025;n/a(n/a).

456. Accardo P, Accardo J, Capute AJ. A neurodevelopmental perspective on the continuum of developmental disabilities. Capute and Accardo's neurodevelopmental disabilities in infancy and childhood. 2008:3-26.

457. Aboelnasr EA, Hegazy FA, Altalway HA. Kinematic characteristics of reaching in children with hemiplegic cerebral palsy: A comparative study. Brain Inj. 2017;31(1):83-9.

458. Baduni K, Mcintyre A, Kjeldsen CP, Marra LR, Kjeldsen WC, Murphy MM, et al. Motor and Cognitive Trajectories in Infants and Toddlers with and at Risk of Cerebral Palsy Following a Community-Based Intervention. Children-Basel. 2024;11(11):1283.

459. Yeom HG, Kim JS, Chung CK. Brain mechanisms in motor control during reaching movements: Transition of functional connectivity according to movement states. Scientific Reports. 2020;10(1):567.

460. Thelen E, Spencer JP. Postural control during reaching in young infants: a dynamic systems approach. Neuroscience & Biobehavioral Reviews. 1998;22(4):507-14.

461. Jaspers E, Desloovere K, Bruyninckx H, Molenaers G, Klingels K, Feys H. Review of quantitative measurements of upper limb movements in hemiplegic cerebral palsy. Gait & Posture. 2009;30(4):395-404.

462. Rozaire J, Paquin C, Henry L, Agopyan H, Bard-Pondarre R, Naaim A, et al. A systematic review of instrumented assessments for upper limb function in cerebral palsy: current limitations and future directions. J Neuroeng Rehabil. 2024;21(1):56.

463. Brown JV, Schumacher U, Rohlmann A, Ettlinger G, Schmidt RC, Skreczek W. Aimed movements to visual targets in hemiplegic and normal children: is the "good" hand of children with infantile hemiplegia also normal? Neuropsychologia. 1989;27(3):283-302.

464. Khan OA, Singh T, Barany DA, Modlesky CM. Accuracy deficits during robotic time-constrained reaching are related to altered prefrontal cortex activity in children with cerebral palsy. J Neuroeng Rehabil. 2024;21(1):216.

465. Lambercy O, Lünenburger L, Gassert R, Bolliger M. Robots for Measurement/Clinical Assessment. In: Dietz V, Nef T, Rymer WZ, editors. Neurorehabilitation Technology. London: Springer London; 2012. p. 443-56.

466. Little CE, Emery C, Black A, Scott SH, Meeuwisse W, Nettel-Aguirre A, et al. Test-retest reliability of KINARM robot sensorimotor and cognitive assessment: in pediatric ice hockey players. J Neuroeng Rehabil. 2015;12:78.

467. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Adv Data. 2000(314):1-27.

468. Veale JF. Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory factor analysis. Laterality. 2014;19(2):164-77.

469. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214-23.

470. Jethwa A, Mink J, Macarthur C, Knights S, Fehlings T, Fehlings D. Hypertonia Assessment Tool. American Psychological Association; 2015 2015/11/09/.

471. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. Journal of Statistical Software. 2017;82(13):1-26.

472. Lenth RV. Emmeans: Estimated marginal means, aka least-squares means. . R package version 1.8.2 ed2022.

473. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen. 2012;141(1):2-18.

474. Rich TL, Menk JS, Rudser KD, Feyma T, Gillick BT. Less-Affected Hand Function in Children With Hemiparetic Unilateral Cerebral Palsy: A Comparison Study With Typically Developing Peers. Neurorehabil Neural Repair. 2017;31(10-11):965-76.

475. Steenbergen B, Meulenbroek RG. Deviations in upper-limb function of the less-affected side in congenital hemiparesis. Neuropsychologia. 2006;44(12):2296-307.

476. Braendvik SM, Elvrum AK, Vereijken B, Roeleveld K. Relationship between neuromuscular body functions and upper extremity activity in children with cerebral palsy. Developmental medicine and child neurology. 2010;52(2):e29-34.

477. Sukal-Moulton T, Krosschell KJ, Gaebler-Spira DJ, Dewald JP. Motor impairments related to brain injury timing in early hemiparesis. Part II: abnormal upper extremity joint torque synergies. Neurorehabil Neural Repair. 2014;28(1):24-35.

478. Pavão SL, Pessarelli Visicato L, da Costa CSN, de Campos AC, Rocha NACF. Effect of the severity of manual impairment and hand dominance on anticipatory and compensatory postural adjustments during manual reaching in children with cerebral palsy. Research in Developmental Disabilities. 2018;83:47-56.

479. Hoare B, Greaves S. Unimanual versus bimanual therapy in children with unilateral cerebral palsy: Same, same, but different. J Pediatr Rehabil Med. 2017;10(1):47-59.

480. Glover S. Separate visual representations in the planning and control of action. Behav Brain Sci. 2004;27(1):3-24; discussion -78.

481. Verrel J, Bekkering H, Steenbergen B. Eye–hand coordination during manual object transport with the affected and less affected hand in adolescents with hemiparetic cerebral palsy. Experimental Brain Research. 2008;187(1):107-16.

482. Olivier I, Baker C, Cordier J, Thomann G, Nougier V. Cognitive and motor aspects of a coincidence-timing task in Cerebral Palsy children. Neurosci Lett. 2015;602:33-7.

483. Volman MJ, Wijnroks A, Vermeer A. Effect of task context on reaching performance in children with spastic hemiparesis. Clinical Rehabilitation. 2002;16(6):684-92.

484. Johansson AM, Domellöf E, Rönnqvist L. Timing training in three children with diplegic cerebral palsy: short- and long-term effects on upper-limb movement organization and functioning. Front Neurol. 2014;5:38.

485. Stuart S, Wagner J, Makeig S, Mancini M. Brain Activity Response to Visual Cues for Gait Impairment in Parkinson's Disease: An EEG Study. Neurorehabil Neural Repair. 2021;35(11):996-1009.

486. Tosserams A, Weerdesteyn V, Bal T, Bloem BR, Solis-Escalante T, Nonnekes J. Cortical Correlates of Gait Compensation Strategies in Parkinson Disease. Ann Neurol. 2022;91(3):329-41.

487. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain. 1995;118 (Pt 4):913-33.

488. Harrison EC, Grossen S, Tueth LE, Haussler AM, Rawson KS, Campbell MC, et al. Neural mechanisms underlying synchronization of movement to musical cues in Parkinson disease and aging. Front Neurosci. 2025;19:1550802.

489. Christensen D, Van Naarden Braun K, Doernberg NS, Maenner MJ, Arneson CL, Durkin MS, et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning - Autism and Developmental Disabilities Monitoring Network, USA, 2008. Developmental medicine and child neurology. 2014;56(1):59-65.

490. Ferrari A, Tersi L, Ferrari A, Sghedoni A, Chiari L. Functional reaching discloses perceptive impairment in diplegic children with cerebral palsy. Gait & Posture. 2010;32(2):253-8.

491. Bishop L, Gordon AM, Kim H. Hand Robotic Therapy in Children with Hemiparesis: A Pilot Study. American Journal of Physical Medicine & Rehabilitation. 2017;96(1):1-7.

492. Gerber CN, Labruyere R, van Hedel HJ. Reliability and Responsiveness of Upper Limb Motor Assessments for Children With Central Neuromotor Disorders: A Systematic Review. Neurorehabil Neural Repair. 2016;30(1):19-39.

493. Bonilauri A, Sangiuliano Intra F, Pugnetti L, Baselli G, Baglio F. A Systematic Review of Cerebral Functional Near-Infrared Spectroscopy in Chronic Neurological Diseases-Actual Applications and Future Perspectives. Diagnostics (Basel). 2020;10(8).

494. Clark K, Squire RF, Merrikhi Y, Noudoost B. Visual attention: Linking prefrontal sources to neuronal and behavioral correlates. Prog Neurobiol. 2015;132:59-80.

495. Shimada S, Hiraki K, Matsuda G, Oda I. Decrease in prefrontal hemoglobin oxygenation during reaching tasks with delayed visual feedback: a near-infrared spectroscopy study. Brain Res Cogn Brain Res. 2004;20(3):480-90.

496. Mazzoli E, Teo WP, Salmon J, Pesce C, He J, Ben-Soussan TD, et al. Associations of Class-Time Sitting, Stepping and Sit-to-Stand Transitions with Cognitive Functions and Brain Activity in Children. Int J Environ Res Public Health. 2019;16(9):1482.

497. Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T, et al. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. Neuroimage. 2004;23(3):1020-6.

498. Strangman G, Culver JP, Thompson JH, Boas DA. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage. 2002;17(2):719-31.

499. Cakar S, Gokalp Yavuz F. Nested and robust modeling techniques for fNIRS data with demographics and experiment related factors in n-back task. Neurosci Res. 2023;186:59-72.

500. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. J R Stat Soc B. 1995;57(1):289-300.

501. Steenbergen B, van Thiel E, Hulstijn W, Meulenbroek RGJ. The coordination of reaching and grasping in spastic hemiparesis. Human Movement Science. 2000;19(1):75-105.

502. Levin MF, Dimov M. Spatial zones for muscle coactivation and the control of postural stability. Brain Res. 1997;757(1):43-59.

503. Davies TC, AlManji A, Stott NS. A cross-sectional study examining computer task completion by adolescents with cerebral palsy across the Manual Ability Classification System levels. Developmental medicine and child neurology. 2014;56(12):1180-6.

504. Fernani D, Prado MTA, da Silva TD, Massetti T, de Abreu LC, Magalhaes FH, et al. Evaluation of speed-accuracy trade-off in a computer task in individuals with cerebral palsy: a cross-sectional study. BMC Neurol. 2017;17(1):143.

505. Hoffman RM, Wilson TW, Kurz MJ. Hand Motor Actions of Children With Cerebral Palsy Are Associated With Abnormal Sensorimotor Cortical Oscillations. Neurorehabil Neural Repair. 2019;33(12):1018-28.

506. Battaglia-Mayer A. A Brief History of the Encoding of Hand Position by the Cerebral Cortex: Implications for Motor Control and Cognition. Cereb Cortex. 2019;29(2):716-31.

507. Lim SB, Eng JJ. Increased Sensorimotor Cortex Activation With Decreased Motor Performance During Functional Upper Extremity Tasks Poststroke. J Neurol Phys Ther. 2019;43(3):141-50.

508. Lee JJ, Lee DR, Shin YK, Lee NG, Han BS, You SJ. Comparative neuroimaging in children with cerebral palsy using fMRI and a novel EEG-based brain mapping during a motor task--a preliminary investigation. NeuroRehabilitation. 2013;32(2):279-85.

509. Vaz DV, Silva PL, Mancini MC, Carello C, Kinsella-Shaw J. Towards an ecologically grounded functional practice in rehabilitation. Human Movement Science. 2017;52:117-32.

510. Leff DR, Elwell CE, Orihuela-Espina F, Atallah L, Delpy DT, Darzi AW, et al. Changes in prefrontal cortical behaviour depend upon familiarity on a bimanual co-ordination task: an fNIRS study. Neuroimage. 2008;39(2):805-13.

511. Nemani A, Yucel MA, Kruger U, Gee DW, Cooper C, Schwaitzberg SD, et al. Assessing bimanual motor skills with optical neuroimaging. Sci Adv. 2018;4(10):eaat3807.

512. Nemani A, Ahn W, Gee D, Intes X, Schwaitzberg S, Yucel M, et al. Objective Surgical Skill Differentiation for Physical and Virtual Surgical Trainers via Functional Near-Infrared Spectroscopy. Stud Health Technol Inform. 2016;220:256-61.

513. Selb J, Yucel MA, Phillip D, Schytz HW, Iversen HK, Vangel M, et al. Effect of motion artifacts and their correction on near-infrared spectroscopy oscillation data: a study in healthy subjects and stroke patients. J Biomed Opt. 2015;20(5):56011.

514. Bostan AC, Strick PL. The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci. 2018;19(6):338-50.

515. Lambrick D, Stoner L, Grigg R, Faulkner J. Effects of continuous and intermittent exercise on executive function in children aged 8-10 years. Psychophysiology. 2016;53(9):1335-42.

516. Chang J-J, Wu T-I, Wu W-L, Su F-C. Kinematical measure for spastic reaching in children with cerebral palsy. Clinical Biomechanics. 2005;20(4):381-8.

517. de los Reyes-Guzmán A, Dimbwadyo-Terrer I, Trincado-Alonso F, Monasterio-Huelin F, Torricelli D, Gil-Agudo A. Quantitative assessment based on kinematic measures of functional impairments during upper extremity movements: A review. Clinical Biomechanics. 2014;29(7):719-27.

518. Langan J, Doyle ST, Hurvitz EA, Brown SH. Influence of task on interlimb coordination in adults with cerebral palsy. Arch Phys Med Rehabil. 2010;91(10):1571-6.

519. Campbell KS, Whitten SVW, Newell KM, Li L, Singh T, Khan OA, et al. Deficits in recovery of postural stability after stepping are limb- and phase-specific in children with unilateral cerebral palsy. Gait & Posture. 2024;114:227-33.

520. van der Heide JC, Hadders-Algra M. Postural muscle dyscoordination in children with cerebral palsy. Neural Plast. 2005;12(2-3):197-203; discussion 63-72.

521. Saavedra S, Joshi A, Woollacott M, van Donkelaar P. Eye hand coordination in children with cerebral palsy. Exp Brain Res. 2009;192(2):155-65.

522. Adamos T, Chukoskie L, Townsend J, Trauner D. Spatial attention in children with perinatal stroke. Behav Brain Res. 2022;417:113614.

523. Faw B. Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: a tutorial review. Conscious Cogn. 2003;12(1):83-139.

524. Franceschini MA, Joseph DK, Huppert TJ, Diamond SG, Boas DA. Diffuse optical imaging of the whole head. J Biomed Opt. 2006;11(5):054007.

525. Zhang Y, Brooks DH, Franceschini MA, Boas DA. Eigenvector-based spatial filtering for reduction of physiological interference in diffuse optical imaging. J Biomed Opt. 2005;10(1):11014.

526. Borrell JA, Fraser K, Manattu AK, Zuniga JM. Laterality Index Calculations in a Control Study of Functional Near Infrared Spectroscopy. Brain Topogr. 2023;36(2):210-22.

527. Jovellar-Isiegas P, Cuesta Garcia C, Jaen-Carrillo D, Palomo-Carrion R, Pena Alonso C, Roche-Seruendo LE. Somatosensation and motor performance in the less-affected and more-affected hand of unilateral cerebral palsy children: a cross-sectional study. Disabil Rehabil. 2023;45(21):3500-10.

528. Malla C, Smeets JBJ, Brenner E. Potential Systematic Interception Errors are Avoided When Tracking the Target with One's Eyes. Sci Rep. 2017;7(1):10793.

529. Babik I. From Hemispheric Asymmetry through Sensorimotor Experiences to Cognitive Outcomes in Children with Cerebral Palsy. Symmetry. 2022;14(2):345.

530. Kaller CP, Rahm B, Spreer J, Weiller C, Unterrainer JM. Dissociable contributions of left and right dorsolateral prefrontal cortex in planning. Cereb Cortex. 2011;21(2):307-17.

531. Mutha PK, Haaland KY, Sainburg RL. The effects of brain lateralization on motor control and adaptation. J Mot Behav. 2012;44(6):455-69.

532. MacNeilage PF, Rogers LJ, Vallortigara G. Origins of the left & right brain. Sci Am. 2009;301(1):60-7.

533. Sauseng P, Feldheim JF, Freunberger R, Hummel FC. Right Prefrontal TMS Disrupts Interregional Anticipatory EEG Alpha Activity during Shifting of Visuospatial Attention. Front Psychol. 2011;2:241.

534. Perlman SB, Luna B, Hein TC, Huppert TJ. fNIRS evidence of prefrontal regulation of frustration in early childhood. NeuroImage. 2014;85:326-34.

535. Calub CA, Rapport MD, Irurita C, Eckrich SJ, Bohil C. Attention Control in Children With ADHD: An Investigation Using Functional Near Infrared Spectroscopy (fNIRS). Child Neuropsychol. 2022;28(8):1072-96.

536. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167-202.

537. Gunadi S, Leung TS, Elwell CE, Tachtsidis I. Spatial sensitivity and penetration depth of three cerebral oxygenation monitors. Biomed Opt Express. 2014;5(9):2896-912.

538. Potgieser AR, de Jong BM, Wagemakers M, Hoving EW, Groen RJ. Insights from the supplementary motor area syndrome in balancing movement initiation and inhibition. Front Hum Neurosci. 2014;8:960.

539. Battaglia-Mayer A, Caminiti R. Corticocortical Systems Underlying High-Order Motor Control. J Neurosci. 2019;39(23):4404-21.

540. Lai YH, Wang ZP, Yue GH, Jiang CH. Determining Whether Tennis Benefits the Updating Function in Young Children: A Functional Near-Infrared Spectroscopy Study. Applied Sciences-Basel. 2020;10(1).

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APPROVAL

July 23, 2019

Dear Christopher Modlesky:

On 7/23/2019, the IRB reviewed the following submission:

Type of Review:	Modification
Title of Study:	Effect of a high-frequency, low-magnitude vibration on muscle properties, physical activity and balance in children with cerebral palsy
Investigator:	Christopher Modlesky
Co-Investigator:	Sydni Wilhoite
IRB ID:	MOD00007255
Funding:	NATIONAL INSTITUTES OF HEALTH
Grant ID:	AWD00007725
Review Category:	Minor Modification

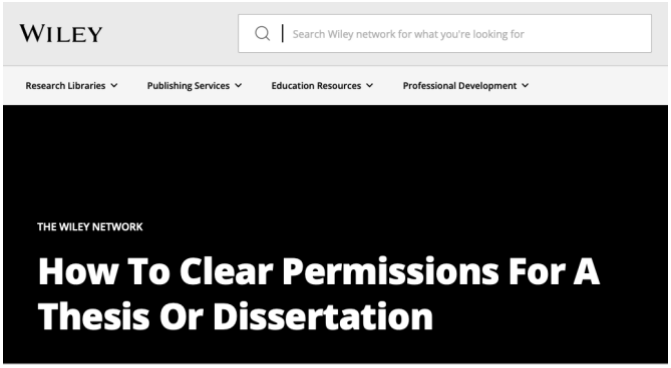
Modifications:

- Added Katelyn Campbell, Owais Khan, and Sydni Wilhoite to the study team.
- Added Barbara Weissman at Emory University and removed Robert Bruce.

Materials Reviewed: Modification form; CITI Training records.

The IRB approved the protocol from 7/23/2019 to 3/5/2020 inclusive. Before or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR.

If continuing review approval is not granted before the expiration date of 3/5/2020 approval of this study expires on that date.



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Leah Alaani, Senior Marketing Manager, Wiley | November 16, 2020

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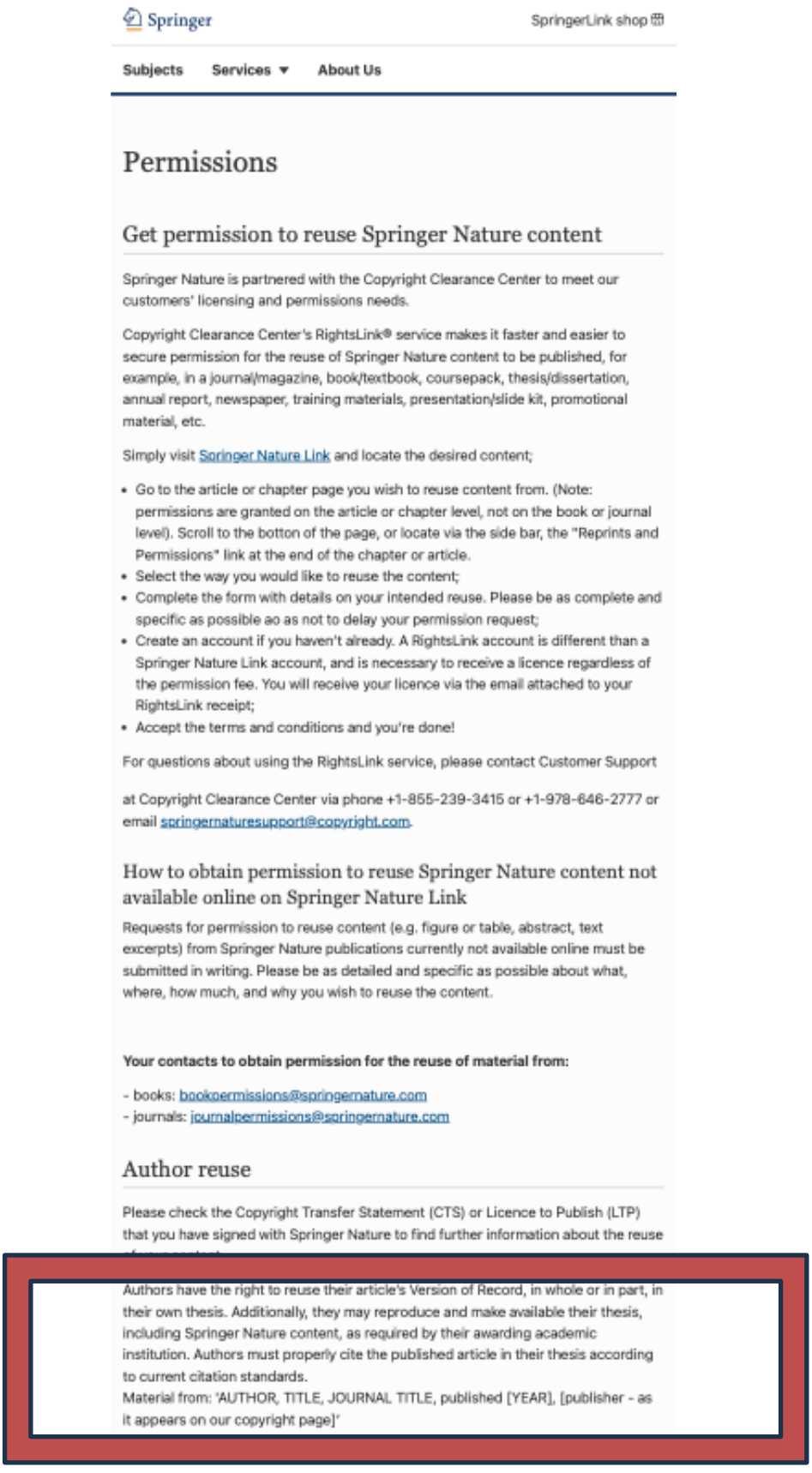

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