Advancing non-invasive neuromodulation clinical trials in children: Lessons from perinatal stroke

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Keywords: Neuroplasticity, Developmental plasticity, Brain stimulation, Cerebral palsy, Perinatal stroke, Transcranial magnetic stimulation, Transcranial direct current stimulation, Clinical trials

Abstract

Applications of non-invasive brain stimulation including therapeutic neuromodulation are expanding at an alarming rate. Increasingly established scientific principles, including directional modulation of well-informed cortical targets, are advancing clinical trial development. However, high levels of disease burden coupled with zealous enthusiasm may be getting ahead of rational research and evidence. Experience is limited in the developing brain where additional issues must be considered. Properly designed and meticulously executed clinical trials are essential and required to advance and optimize the potential of non-invasive neuromodulation without risking the well-being of children and families. Perinatal stroke causes most hemiplegic cerebral palsy and, as a focal injury of defined timing in an otherwise healthy brain, is an ideal human model of developmental plasticity. Advanced models of how the motor systems of young brains develop following early stroke are affording novel windows of opportunity for neuromodulation clinical trials, possibly directing neuroplasticity toward better outcomes. Reviewing the principles of clinical trial design relevant to neuromodulation and using perinatal stroke as a model, this article reviews the current and future issues of advancing such trials in children.

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1. First principles of neuromodulation clinical trials

Non-invasive brain stimulation applications are exploding. There is great and justified concern that the rate of growth in the number of brains being stimulated is already far exceeding the level of science that supports the approach. There are major issues of unregulated use across broad and often vulnerable populations with immoral marketing of unproven, potentially dangerous devices. Examples range from shameless promotion of enhanced gaming performance to teenagers to do it yourself tDCS machines being made in people's basements. Ethical issues specific to the application of brain stimulation in children must also be considered. For these reasons, and in order to advance the responsible scientific study of neuromodulation in the developing brain, several principles merit discussion here.

It is highly unlikely that introducing a focal magnetic field or local current into a functional area of human cortex will...
magically create new, clinically relevant function. Instead, an endogenous substrate for neuroplasticity that might be altered by such neuromodulation seems a much more likely mechanism by which brain stimulation might produce lasting, therapeutic alterations in brain function. This fundamental tenet also helps correct for the known and large heterogeneity between subjects inevitably enrolled in such trials. That a TMS measurement as simple as the rest motor threshold can range from 20 to over 60% of maximum stimulator output across a sample of normal subjects of the same age and gender points to an even more enormous inter-subject variability in clinically diseased populations. However, if such subjects share fundamental neuroplasticity mechanisms within their cortex (e.g. long term potentiation) and are induced to activate them in the context of desired, functional activity, the potential for neuromodulation is likely greater.

In a similar context, an informed cortical target for modulation is also essential. Identification of such functionally relevant cortical regions is often difficult. As outlined below, studies of enhancement of motor learning with brain stimulation have often logically targeted the primary motor cortex. This has logically extended to clinical populations with motor disability, targeting the motor cortex and related network components in common populations of motor disability such as adult stroke hemiparesis. Importantly, this evolving process has not rested on such simplistic anatomical localization alone. Instead, neurophysiological models have been developed to first understand what happens to the system of interest in the disease state. These often include large bodies of evidence from preclinical animal models combined with human studies using advanced neuroimaging and other neurophysiology tools. Such an example for perinatal stroke will be presented below.

Such models not only identify potential targets but also a desired direction for change. For example, the lesioned motor cortex may be underactive while the homologous region of the contralateral, non-lesioned hemisphere may be relatively overactive. Such a model of “imbalance interhemispheric motor inhibition” is probably over simplified but is well supported by large volumes of neurophysiological evidence and has driven the majority of non-invasive brain stimulation trials in adult stroke. Recent summative evidence of rTMS therapeutic trials highlights this point by comparing modalities and targets across a wide range of such conditions.

Importantly, each these three principles of modulating an informed target in a specific direction during activation of endogenous plasticity are arguably still not well defined in relatively concrete examples like adult stroke. In fact, such principles are often not entirely obvious (or even theoretically well defined) in many other stimulation clinical trials. While such failure should raise immediate concerns of validity, their presence is relatively sparse in the most defined therapeutic non-invasive brain stimulation population: adult major depression. High frequency rTMS of the dominant dorsolateral prefrontal cortex (DLPFC) is FDA and Health Canada approved and rapidly expanding as an insured service. While based on some human evidence of regional dysfunction in this broad, highly connected area with functional implications for some symptomology, it could be argued that the ability of depression to satisfy the above criteria is modest at best.

This raises a final principle consideration of disease specificity. As a very common, disabling, and highly studied disease, major depression carries well-defined diagnostic and classification criteria. Despite this, there are innumerable factors, both measureable and unknown, that would likely influence response to neuromodulation. In contrast, autism is a heterogeneous disorder of social and communication development that is likely due to hundreds of different genetic disorders in addition to other etiologies. This does not mean that informed, symptom-specific targeting of cortical regions to enhance other therapies or learning is impossible. However, the breadth of heterogeneity must be acknowledged and adjusted for whenever possible if meaningful trials are to be designed. Trials of autism due to one specific mutation bring limitations of recruitment and sample size and are still not ideal; consider the phenotypic variability of tuberous sclerosis alone. However, striving for disease specificity whenever possible will likely advance progress in paediatric neuromodulation trials much faster. Extricating the very specific forms of perinatal stroke from the more complex world of cerebral palsy for motor learning neuromodulation trials provides a practical example.

2. Perinatal stroke

You will not likely incur a higher period of risk for ischaemic stroke than the week you are born. A term newborn carries a risk >1:3500, three-fold higher than a week in the life of a diabetic, hypertensive, smoking adult and eight-fold above all adults. An additional 50% of perinatal stroke presents later in infancy. Perinatal stroke is the leading cause of hemiplegic cerebral palsy (HCP) and most survivors suffer additional neurological sequelae including intellectual disabilities, language impairments, developmental and behavioural disorders, and epilepsy. Frequent occurrence combined with lifelong morbidity generates large global burdens. Identification of a causative factor remains elusive in most cases and with no means of prevention, perinatal stroke and HCP will burden thousands of children for decades to come.

An essential first step in improving outcomes from perinatal brain injury is to understand the underlying disease. We have defined distinct clinical-radiographic perinatal stroke syndromes, refining perinatal stroke research toward specific disease states. Two main types predominate. These are summarized in Fig. 1. We have validated this imaging-based classification system and demonstrated it’s research applications including the prediction of long-term neurological outcomes, recognition of novel risk factors, imaging markers of disease processes, and new targets for therapeutic interventions. Arterial ischaemic strokes (AIS) are large brain injuries secondary to occlusion of major cerebral arteries. Some present at birth with acute seizures (called symptomatic neonatal AIS) while others are not recognized until infancy when hemiparesis becomes evident (called arterial presumed perinatal ischaemic stroke). In contrast, periventricular venous infarctions (PVI) are subcortical white matter lesions acquired well before birth. Secondary to germinal matrix bleeds with subsequent medullary venous infarction, these lesions occur in utero before 34 weeks.
gestation. MRI work by our group and others can detect these remote foetal bleeds, facilitating accurate diagnosis. Our recent work has begun elucidating the pathophysiological and plasticity mechanisms in PVI. Our imaging and population-based data suggest AIS and PVI prevalence are similar. Most relevant here, both AIS and PVI injure primary components of the motor system early in life, resulting in HCP. This commonality of focal motor injury in a healthy brain, combined with distinct differences in lesion timing and location, makes perinatal stroke the ideal human model for the study of developmental plasticity.

3. Perinatal stroke outcomes

Neurodevelopmental deficits occur in ~75% of perinatal stroke survivors. Hemiparetic CP is the most common term-born cerebral palsy and stroke is the leading cause. Motor deficits are the most prominent and disabling symptom, present in 30–60% of acute symptomatic NAIS and >80–90% of presumed perinatal ischaemic strokes including PVI. Clinical, laboratory, and EEG variables are limited in their abilities to predict motor outcome, but neuroimaging has improved the early identification of the most affected children. We and others have described how corticospinal tract diffusion MRI in NAIS and structural MRI in PPIS can predict motor outcomes in infancy. This has opened the window for intervention earlier in development. Deficits in language, vision, cognition, behaviour and epilepsy also occur, present in 20–60% of arterial strokes. The morbidity of perinatal stroke lasts a lifetime, amplifying the burden on child, family, and society. Physical disability contributes across this realm of consequences and current interventions have limited efficacy. There is therefore an urgent need for new treatment strategies founded upon our best possible understanding of the neurophysiology that underlies the clinical dysfunction.

Fig. 1 – Developmental plastic motor organization following perinatal stroke. (A) Arterial perinatal strokes (NAIS or APPIS) acquired near term result in damage to cortical and subcortical structures. (B) Periventricular venous infarction (PVI) are acquired in utero prior to 34 weeks gestation resulting in isolated injury to the subcortical white matter. Both lesions damage corticospinal tracts, leading to contralateral hemiparetic CP. (C) Animal and human evidence has constructed working models of developmental motor organization following such early unilateral injury. Control of the weak right hand (W) often relies on both contralateral corticospinal pathways from the left (lesioned) motor cortex (LM1) and ipsilateral projections from the unlesioned (right) motor cortex (RM1, dashed line). These two inputs compete to establish synapses with anterior horn spinal motor neuron pools (circles) during development. Each M1 may also influence the other via IHI (coloured dashed arrows). The relative interhemispheric balance is associated with clinical function with contralateral control associated with better function. Interventions that promote the success of contralateral (or inhibit the success of ipsilateral) upper motor neuron systems to compete for spinal motor neurons could result in better motor function.
In 1936, Kennard described better outcomes in younger primates following unilateral motor cortex lesions.\(^5^2\) This Kennard principle has fostered efforts to understand and harness age-related plasticity. Common occurrence and focal injury in an otherwise healthy brain makes perinatal stroke an ideal human model. Terms like “repair” and “reorganization” imply the existence of inherent restorative mechanisms that evolutionary models suggest would not exist.\(^{53}\) Instead, plastic adaptation may represent alterations of normal, ongoing developmental processes occurring after injury. Elegant animal work and human studies have solidified a model that creates novel avenues for therapeutic interventions in hemiparetic CP.\(^{54–56}\) The model consists of 3 primary components (see Fig. 1): The lesioned (A) and non-lesioned (B) motor cortex (and their intra and inter-hemispheric connections) and their influence on spinal motor neuron pools (C).

A. The lesioned hemisphere: contralateral projections to the paretic hand. Adult stroke and animal studies suggest that, on average, motor control in the lesioned hemisphere is associated with better function.\(^{57–61}\) A small childhood stroke study showed that recruitment of perilesional motor area may be associated with higher function.\(^{62}\) We have further correlated the presence of contralateral projections from the lesioned hemisphere with better function.\(^{63,64}\) Rare hemiparetic CP studies have shown decreased excitability in the lesioned hemisphere\(^{65}\) while maintained motor activations approximate typical motor areas.\(^{66}\) PVI-like lesions have associated this contralateral arrangement with better function.\(^{67}\) Small studies have suggested rehab-induced clinical gains may be associated with increases in lesioned motor cortex activations in HCP.\(^{68,69}\) Enhancing motor control in the lesioned hemisphere should favor improved function.

B. Role of the unlesioned hemisphere: ipsilateral projections to the paretic hand. Abnormal projections from the unlesioned hemisphere to the paretic hand are common in hemiparetic CP\(^70–75\) but inconsistent in their physiology.\(^70–73,76–78\) Ipsilateral projections are present in equal proportion at birth but are subsequently withdrawn during normal development.\(^79\) Ipsilateral projections likely arise from homologous regions of primary motor cortex (M1).\(^76,77,113\) Our work suggests the same in both childhood\(^4,78\) and perinatal stroke.\(^81\) In HCP,\(^70–74,77,114\) arterial\(^73–75,82,174\) and PVI-like lesions\(^73,74\) ipsilateral projections are associated with poorer motor function. Over-activity of the non-lesioned M1 may be associated with larger deficits.\(^77,73,82\) In the largest TMS study of perinatal stroke (\(n = 52\)), we recently described the neurophysiology of the contralesional hemisphere, validating many of these observations (Zewdie et al., under review).

Recruitment of ipsilateral projections may therefore represent an example of maladaptive plastic organization not compatible with normal hand function. A pathologically overactive contralesional M1 controlling the ipsilateral weak hand represents a potential therapeutic target in hemiparetic CP.\(^55,84\) Decreasing pathological overactivity of non-lesioned M1 may enhance motor learning in adult stroke.\(^85–88\) In the original Kennard experiments, lesioning the contralesional M1 months after initial injury in young primates improved function of the originally paretic limb.\(^52\) Complex cortical motor circuits within and between the hemispheres also mediate neuroplasticity including interhemispheric inhibition (IHI)\(^89,90\) and intracortical inhibitory and facilitatory circuits.\(^85,91,92\) Alterations in these have provided insight to adult stroke recovery.\(^93–97\) Each of these model components represent neurophysiological outcomes measurable with modern technologies (below).\(^98\) We have measured such systems in children with paediatric\(^99\) and perinatal\(^101\) stroke, confirming their relevance to clinical function.

C. Synaptic competition model. The target of these developing upper motor neuron systems are the spinal lower motor neurons, control of which determines function. Continuous competition between contralateral and ipsilateral corticospinal tract projections to establish synapses with these cells occurs through development with eventual contralateral domination and withdrawal of ipsilateral projections.\(^54,55\) Primate studies confirm a protracted developmental period for such organization\(^56,100–102\) spanning childhood and into adulthood.\(^103\) Injury likely reduces the normal contralateral advantage, allowing ipsilateral projections to establish control in more severe hemiparetic CP.

Cortical stimulation or inhibition can modulate this process. Pharmacological inhibition of M1 alters spinal motor neuron innervation and enhances ipsilateral projections\(^104,105\) as seen in hemiparetic CP.\(^55\) Daily M1 electrical stimulation can also preserve the corticospinal connections normally withdrawn during early development in cats.\(^106\) These findings complement evidence of activity-dependent enhancement of corticospinal connections in animal,\(^107\) histopathological,\(^108\) and neurophysiological studies.\(^71,72\) Interventional strategies to enhance contralateral (or inhibit ipsilateral) corticospinal projections might therefore enhance motor development and function.\(^96\) This might be achieved in two ways — stimulation of the lesioned M1 or inhibition of the unlesioned M1. The latter approach carries stronger animal evidence\(^109\) with authors concluding that “activity-dependent processes later in development can be harnessed to restore a more normal pattern of corticospinal connectivity and function.”

5. The window of opportunity in developmental neuroplasticity

Modern definitions of CP suggest deficits are static and non-progressive.\(^110\) However, neonates with stroke usually demonstrate no observable neurological deficits.\(^111\) Asymmetry is not appreciated until 4–6 months\(^112,113\) with the full severity typically appreciated years later.\(^114\) Consistent with
the model above, progressive loss of contralateral control through early development may result in imbalance of cortical control and motor networks, resulting in impaired function. Both animal\textsuperscript{100,111} and TMS studies of motor development by ourselves\textsuperscript{99} and others\textsuperscript{73,112} agree that plastic motor organization continues well beyond adolescence. New trials are proving that the plasticity of even the aged adult brain is modifiable with multiple interventions.\textsuperscript{113} Whether or not the optimal window for interventional modulation suggested in animal models falls within the earliest years of human development remains to be determined. Before brain stimulation can be advanced toward this very young age of possible maximal plasticity, the neurophysiology, efficacy, and safety of modulatory interventions must first be established in older children. Hence, school age children represent the ideal population in which brain stimulation and modulation of brain plasticity should be explored. Before invasive, permanent interventions (e.g. stem cells)\textsuperscript{114} can be advanced, non-invasive means need to demonstrate efficacy of the approach while elucidating the neurophysiological principles on which they are based.

6. Therapeutic neuromodulation in hemiparetic CP

6.1. Intensive motor learning, manual therapy

Owing to an increasing number of clinical trials, evidence for emerging hemiparetic CP therapies is increasing. Constraint induced movement therapy (CIMT) promotes functional use of an impaired limb by constraint of the less-impaired limb coupled with repetitive motor practice.\textsuperscript{113,115–118} In adult stroke, 2 weeks of CIMT can generate gains lasting years.\textsuperscript{113,118,119} Multiple paediatric trials support CIMT effectiveness in hemiparetic CP.\textsuperscript{51,120–128} Consistent with the model below, functional imaging suggests CIMT shifts motor function toward the lesioned hemisphere.\textsuperscript{68,129–132} CIMT-induced cortical reorganization has been demonstrated in adults with fMRI\textsuperscript{68,130,133–135} and TMS\textsuperscript{129,136–142} and small hemiparetic CP studies.\textsuperscript{68,69,132} CIMT limitations include a somewhat invasive nature and the exclusion of bimanual learning. Bimanual approaches can also improve function in hemiparetic CP trials.\textsuperscript{143,144} Hand-arm Intensive Bimanual Therapy (HABIT) is an evidence-based, safe, valid, and effective motor learning therapy in children with hemiparetic CP.\textsuperscript{124,144–147} Efficacy appears equal to CIMT\textsuperscript{144} but the absence of constraint facilitates functional bimanual motor learning and removes the complications of casting in our outpatient population. Comparisons of CIMT and HABIT suggest possible greater achievement of self-directed goals with HABIT.\textsuperscript{144} Models for intensive motor learning may combine approaches with early CIMT (e.g. week 1) to induce new functions in the paretic limb followed immediately (week 2) by bimanual therapy to encourage incorporation of new function into more functional tasks. How such therapies are delivered has also evolved. Intensive, camp-based models are increasingly popular, both for psychosocial and programming benefits but also to deliver high doses of structured motor learning therapy that may optimize use-dependent changes in brain plasticity and function. Such programs should be based on best available evidence and structured according to standardized elements such as the TIDIER criteria.\textsuperscript{105} Consistency of intensity, dosing, and methodology can be increased by strict adherence to a manual of operations by a limited number of trained therapists.\textsuperscript{144} Structured home programs based on the same principles with ongoing therapist support may be provided during longer-term follow-up periods. Therapy programs should be designed and delivered by experienced paediatric occupational therapists. The cost of using such highly qualified personnel for so many hours of 1:1 therapy may be restrictive. We recently used final year therapy students supervised by 2 experienced paediatric OT’s to deliver such therapy in camp model with good success, broader knowledge translation to learners, and much lower costs.

Providing such intensive, goal-directed, evidence-based therapy to all participants provides numerous potential advantages. These go beyond the primary principle above that an endogenous substrate for plastic change may well be an essential requirement for brain stimulation to be effective. That all subjects receive individualized, “best available” treatment facilitates randomization to such additional interventions where there is equipoise regarding efficacy and minimal, but not zero, risk of adverse events. It creates opportunity for active, motivated participation focused on aims that matter to the individual patient. Limitations include the dosage of therapy achieved over focused time frames where the optimal number of hours, both total and divided between focused and more general training, remain to be determined. The balance of unimanual versus bimanual and the timing of how the two should be integrated is also imprecise and in need of better evidence. Lastly, the potential psychological and social benefits of such group-based participation with grouping of participants by developmental level should not be underestimated. This may be optimized by inclusion of group activities within camp based day programs or, alternatively, incorporated into smaller time frames within after school programs, possibly with the addition of group weekends sessions. When asked, most children with hemiparesis have not previously met a peer with the same disability. Working together to achieve personal goals alongside similarly affected, motivated peers likely carries large psychosocial benefits, the more accurate measurement of which is a goal of future trials.

As outlined below, we have completed two clinical trials of non-invasive brain stimulation in children with perinatal stroke and hemiparesis. This included a total of 68 participants between the ages of 6 and 18 years: 45 in an rTMS trial\textsuperscript{105} and 24 in a tDCS intervention (unpublished). All participated in child-centred, goal-directed, age-appropriate intensive motor learning programs over 2 weeks.

6.2. Non-invasive brain stimulation: repetitive transcranial magnetic stimulation (rTMS)

TMS given repeatedly can produce lasting changes in brain function. rTMS studies have established this principle in health and disease over the past 20 years\textsuperscript{148–150} with recent evidence-based summaries of therapeutic efficacy.\textsuperscript{3} High
frequency rTMS (~10 Hz) stimulates cortex which both animal\textsuperscript{151–154} and adult\textsuperscript{148} stroke studies suggest can facilitate motor function. Similarly, low frequency rTMS (~1 Hz) typically inhibits cerebral cortex though there are exceptions to both these rules.\textsuperscript{155–157} rTMS is amenable to randomized, sham-controlled clinical trials.\textsuperscript{158} Accumulating evidence suggests rTMS can modulate neural networks\textsuperscript{159} to enhance motor function in chronic adult stroke.\textsuperscript{160,161} Limitations of rTMS include very focal administration and burdensome, immobile hardware that prevents simultaneous rehabilitation and co-activation of endogenous motor learning systems.

Despite both the high burden of motor disability and greater brain plasticity in children, rTMS studies have been limited. Completed rTMS studies have reported favourable tolerability with no significant adverse events.\textsuperscript{162–164} Daily rTMS for weeks in animals,\textsuperscript{165} adults with stroke\textsuperscript{149,160,166–170} and our recent paediatric stroke trials\textsuperscript{53,81,160,171} further support this safety. Evidence from our group and others has shown no adverse effect of non-lesioned M1 inhibitory rTMS on normal (unaffected) hand function in hemiparetic subjects.\textsuperscript{57,63} We completed the first paediatric rTMS randomized trial where 8 days of non-lesional inhibitory rTMS improved hand function in with chronic subcortical stroke acquired during childhood.\textsuperscript{53}

We recently completed the PLASTIC CHAMPS trial (Fig. 3).\textsuperscript{172} This was a factorial, controlled randomized trial designed to test the ability of contralesional, inhibitory rTMS and CIMT to enhance motor learning in children with perinatal stroke and hemiparesis. Forty-five children aged 6–18 years completed all outcome measures from baseline to 6 months. There were no serious adverse events or drop outs and tolerability measures were favourable. An additive effect of rTMS and CIMT was observed on the primary objective outcome of change in AHA at 6 months where the addition of both therapies more than doubled the chances of a clinically significant improvement (Fig. 2). Subjective, psychosocial and quality of life gains were also observed. This trial also confirmed the feasibility of measuring both baseline AND post-intervention plastic neurophysiology using advanced imaging and TMS neurophysiology (see below). This trial provides class II evidence for rTMS and CIMT enhancement of motor learning therapy while supporting the overall safety and feasibility of conducting non-invasive stimulation trials in children with perinatal stroke-induced hemiparesis.

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**Fig. 2** – Timeline of evaluations, interventions, and outcomes. Baseline neurophysiology and motor function studies are performed within a month of intervention. HABIT therapy (90 min) with TDCS or sham (first 30 min) intervention occurs daily for 10 consecutive weekdays. Both Jebsen Taylor hand function test (JT) and safety outcomes (S) are evaluated daily. All outcomes are repeated the week following intervention. Patients enter a home maintenance therapy program with clinical outcomes restated at 2 and 6 months. See text for details. *Abbreviations:* fMRI: Functional MRI; rsfMRI: Resting state fMRI; TMS: Transcranial magnetic stimulation; TDCS: Transcranial direct current stimulation; HABIT: Hand-arm bimanual intensive therapy; AHA: Assisting Hand Assessment; COPM: Canadian occupational performance measure; TST: TDCS safety test; JT: Jebsen Taylor Test of Hand Function; MA: Melbourne Assessment of Unilateral Upper Extremity Function; BB: Box and blocks test; PP: Perdue pegboard test; PMAL: Paediatric Motor Activity Log; QOL: Quality of life measures.
6.3. Non-invasive brain stimulation: transcranial direct current stimulation (tDCS)

tDCS applies scalp electrodes (anode and cathode) to generate weak direct currents (1–2 mA) that induce polarity-dependent changes in brain excitability. tDCS induces regional, transient modulation of resting membrane potential and cortical neuronal excitability. In general, anodal stimulation increases cortical excitability while cathodal stimulation decreases it. Modern commercial tDCS systems are painless, inexpensive, and portable, allowing patients to remain mobile during active rehabilitation. tDCS safety and tolerability in adults is well established with thousands of tested and published safety guidelines. Seizure or other serious adverse events have not been reported. Subjects may report mild, transient tingling or itching during the first minute of tDCS current escalation. This sensation can be mimicked in sham experiments, making tDCS amenable to blinded, randomized trials. A published consensus statement endorses the ability of tDCS to enhance motor learning (and other brain functions) in healthy and diseased adults when administered briefly over the motor cortex. Adult studies have not only demonstrated enhanced motor skill learning with contralateral anodal or ipsilateral cathodal tDCS but are also elucidating the mechanisms of neuroplasticity involved. The duration of effect clearly outlasts tDCS interventions by hours to days in a dose dependent fashion, confirming a therapeutic potential.

Recent trials provide Class I evidence that tDCS can enhance motor recovery in adults with chronic stroke (see Table 1). Though fundamental mechanisms may differ, the same approach outlined above stimulating the lesioned, or inhibiting the unlesioned hemisphere, (or both) appears to enhance motor function. For example, Lindenberg et al. studied 20 chronic, hemiparetic stroke patients. Five days of structured therapy (60 min) was combined with 30 min of bilateral anodal (lesioned M1) and cathodal (non-lesioned M1) tDCS. Outcomes included validated stroke motor function measures and pre and post-intervention fMRI neurophysiology. Collectively, such studies support the feasibility, safety, and potential of our proposed study and provide a solid foundation for design, stimulation parameters, and outcome measures. They also highlight directions for advancement –
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<th>Site</th>
<th>tDCS</th>
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<th>Results summary</th>
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<td>Hummel, 2005</td>
<td>Chronic</td>
<td>6</td>
<td>AA</td>
<td>25 cm²; 1 mA; 20 min</td>
<td>JTT practice</td>
<td>JTT, TMS</td>
<td>JTT improved with AA, outlast stim period. AA increased cortical excitability</td>
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<td>1</td>
<td>AA</td>
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<td>JTT practice</td>
<td>JTT, pinch force, reaction time, TMS</td>
<td>Improved JTT, reaction time, and increase cortical excitability</td>
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<td>Hummel, 2006</td>
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<td>AA</td>
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<td>AA shortened reaction time and increased pinch force relative to S</td>
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<td>Hesse, 2007</td>
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<td>FM</td>
<td>3/10 improved in FM</td>
<td>Both AA and CU improved JTT compared to sham</td>
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<tr>
<td>Boggio, 2007</td>
<td>Chronic</td>
<td>9</td>
<td>AA</td>
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<td>JTT</td>
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<tr>
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<td>tDCS + PNS improved key stroke accuracy compared to sham conditions or tDCS alone. Maintained 1 and 6 days after training.</td>
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<td>10</td>
<td>AA</td>
<td>25 cm²; 1 mA; 20 min</td>
<td>BBT, finger acceleration</td>
<td>AA improved BBT and finger acceleration to a greater extent than S. BBT improvements lasted at least 60 min post-stim</td>
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<td>Subacute</td>
<td>19</td>
<td>AA</td>
<td>25 cm²; 2 mA; 20 min; 10 days</td>
<td></td>
<td>FM, BI</td>
<td>Both AA improved FM and WMFT compared to sham. Improved FM and WMFT compared to sham. Improvements lasted at least 1 week</td>
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<td>Lindenberg 2010</td>
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<td>Mahmoudi 2011</td>
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<td>10</td>
<td>AA + CU</td>
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<td>JTT</td>
<td></td>
<td>Improvements with AA + CU, AA and CU. No improvements with AA (extra-ceph) or S</td>
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<tr>
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<td>Chronic</td>
<td>14</td>
<td>AA</td>
<td>1 mA; 30 min; 5 days</td>
<td>OT for 60 min/day; 5 days</td>
<td>ROM, FM, fMRI</td>
<td>CU resulted in greater improvements in ROM and FM than sham. Effects lasted at least one week. Decreased fMRI activation in contralesional motor region</td>
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<tr>
<td>Hesse 2011</td>
<td>Subacute</td>
<td>96</td>
<td>AA</td>
<td>35 cm²; 2 mA; 20 min; daily</td>
<td>20 min robot; 30 sessions</td>
<td>FM, muscle strength and tone, BI, BBT</td>
<td>All groups improved, no effect between interventions</td>
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<tr>
<td>Study (Year)</td>
<td>Type</td>
<td>Group Size</td>
<td>Motor Area</td>
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<tr>
<td>Bolognini 2011 275</td>
<td>Chronic</td>
<td>14</td>
<td>AA + CU</td>
<td>35 cm²; 2 mA; 40 min</td>
<td>CIMT 14 days</td>
<td>JTT, pinch and grip strength, MALS, FM, TMS</td>
<td>JTT, strength, MALS, FM improved with tDCS. Increased lesioned M1 excitability</td>
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<tr>
<td>Stagg 2012 276</td>
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<td>13</td>
<td>AA + CU</td>
<td>35 cm²; 1 mA; 2 min</td>
<td>PT/OT 60 min/day; 10 days (re-assess at 5 days)</td>
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<td>1.5 mA; 30 min</td>
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<td>Finger tapping, pinch force, TMS</td>
<td>rTMS-tDCS enhanced pinch force, but had no effect on finger tapping. Changes in TCI</td>
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<td>Rossi 2013 279</td>
<td>Acute</td>
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<td>FM, NIHSS</td>
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<td>Zimerman 2012 280</td>
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<td>CU</td>
<td>25 cm²; 1 mA; 20 min</td>
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<td></td>
<td>CU enhanced motor skill compared to S. Correlation between SICI and enhancement.</td>
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<td>Wu 2013 281</td>
<td>Subacute</td>
<td>90</td>
<td>CA (S1) S (S1)</td>
<td>25 cm²; 1.2 mA; 20 min; 5x/wk × 4 wk</td>
<td>PT; 30 min twice a day, 5x/wk × 4wk</td>
<td>MAS, FM, BI</td>
<td>More clinical important differences with active tDCS compared to sham post-treatment and at 4 week follow up.</td>
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<td>Ochi 2013 282</td>
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<td>AA + CU</td>
<td>35 cm²; 1 mA; 10 min; 5 days</td>
<td>Robot-assisted arm training; 5 days</td>
<td>FM, MAS, MAL</td>
<td>Both tDCS conditions improved FM and MAS, but no MAL tDCS enhanced circuit task online learning, with retention at 1 week. Improved PPT scores with tDCS</td>
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<tr>
<td>Lefebvre 2013 283</td>
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<td>AA + CU</td>
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<tr>
<td>Fusco 2013 284</td>
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<td></td>
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<td>AA improved 9-hole peg test, CU improved strength. No improvements with bilateral.</td>
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<tr>
<td>Lefebvre 2014 285</td>
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<td>40</td>
<td>AA + CU</td>
<td>35 cm²; 2 mA; 25 min; 6 days</td>
<td>Therapy 1 h after tDCS; 30 min</td>
<td>NIHSS, BI, muscle strength; TMS</td>
<td>All groups improved (smaller improvements in muscle strength). No difference between AA and CU, but both better than S. Increased cortical excitability in lesioned M1</td>
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<tr>
<td>O’Shea 2014 287</td>
<td>Chronic</td>
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<td>AA + CU</td>
<td>35 cm²; 1 mA; 20 min</td>
<td></td>
<td>Reaction time</td>
<td>AA + CU had no effect on reaction time compared to sham, whereas AA and CU did quicken RT.</td>
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<td>Robot; TMS</td>
<td>Movement speed improved. Smoothness improved with tDCS. tDCS after practice reduced speed. Increased cortical excitability. Both AA and S improved dexterity. No chance in hand force.</td>
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<td>Fusco 2014</td>
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<td>?</td>
<td>PT</td>
<td>?</td>
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<tr>
<td>Lee 2014</td>
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<td>CU S</td>
<td>25 cm², 2 mA; 20 min; 15 days</td>
<td>VR therapy, 30 min/day</td>
<td>MAS, manual muscle test, manual function test, FM, BBT, BI</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<td>Cha 2014</td>
<td>Chronic</td>
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<td>35 cm²; 1 mA; 20 min; 20 days</td>
<td>30 min/day</td>
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<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<td>Fusco 2014</td>
<td>Subacute</td>
<td>11</td>
<td>CU S</td>
<td>35 cm²; 1.5 mA; 10 min; 10 days (1/day)</td>
<td>45 min x 2/day x 10 days</td>
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<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<tr>
<td>Au-Yeung 2014</td>
<td>Chronic</td>
<td>10</td>
<td>AA CU S</td>
<td>35 cm²; 1 mA; 20 min; 1 day</td>
<td>VR therapy, 30 min/day</td>
<td>VR therapy, 30 min/day</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<td>Gillick 2015</td>
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<td>13</td>
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<td>CIMT + therapy; 1.5 h per day</td>
<td>ARAT; 9-hole peg test; grip strength; MAL, NIH, TMS</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<tr>
<td>Goh 2015</td>
<td>Chronic</td>
<td>10</td>
<td>AA S</td>
<td>1 mA; 20 min</td>
<td>VR therapy, 30 min/day</td>
<td>VR therapy, 30 min/day</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<tr>
<td>Di Lazzaro 2014</td>
<td>Acute</td>
<td>14, 20</td>
<td>AA + CU S</td>
<td>35 cm²; 2 mA; 40 min; 5 days</td>
<td>CIMT + therapy; 1.5 h per day</td>
<td>ARAT; 9-hole peg test; grip strength; MAL, NIH, TMS</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
</tr>
<tr>
<td>Lefebvre 2015</td>
<td>Chronic</td>
<td>19</td>
<td>AA + CU S</td>
<td>35 cm²; 1 mA; 30 min</td>
<td>Trained circuit task</td>
<td>PPT, circuit task</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
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<td>Sattler 2015</td>
<td>Acute</td>
<td>20</td>
<td>AA + PNS S</td>
<td>35 cm²; 1.2 mA; 13 min; 5 days</td>
<td>CIMT + therapy; 1.5 h per day</td>
<td>ARAT; 9-hole peg test; grip strength; MAL, NIH, TMS</td>
<td>Both groups improved outcome scores. tDCS improved BBT and FM more than training alone.</td>
</tr>
<tr>
<td>Cho 2015</td>
<td>Chronic</td>
<td>27</td>
<td>AA S</td>
<td>35 cm²; 2 mA; 20 min; 18 days (3 x 6 weeks)</td>
<td>Mirror therapy or none (control); 18 days (3 x 6 weeks)</td>
<td>BBT. FM, JTT, grip strength</td>
<td>Control groups improved grip strength and JTT. Greater improvements in BBT and grip strength with tDCS compared to sham.</td>
</tr>
<tr>
<td>Rocha 2016</td>
<td>Chronic</td>
<td>21</td>
<td>AA CU S</td>
<td>35 cm²; 1 mA; 13 min (for AA) or 9 min (for CU); 3x/ wk for 4 wks</td>
<td>CIMT; 6 h/day for 3 wk 1 h of PT daily 3x/wk for 4 wk</td>
<td>CIMT; 6 h/day for 3 wk 1 h of PT daily 3x/wk for 4 wk</td>
<td>Increased in FM for active tDCS groups. All groups equally improved MAL and grip strength.</td>
</tr>
<tr>
<td>Study</td>
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<td>Stimulation Parameters</td>
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<tr>
<td>Straudi 2016</td>
<td>Acute - Chronic</td>
<td>23</td>
<td>AA + CU 35 cm², 1 mA, 30 min; 10 days</td>
<td>Robot-assisted therapy; 10 days</td>
<td>FM, BBT, MAL</td>
<td>Both groups improved FM, but no difference between AA and S. Patients with chronic subcortical strokes benefited more than those with acute and cortical stroke however. ARAT WMFT showed improvements up to 3 months post-training with AA</td>
<td></td>
</tr>
<tr>
<td>Allman 2016</td>
<td>Chronic</td>
<td>24</td>
<td>AA 35 cm²; 1 mA; 20 min; 9 days</td>
<td>Motor training; 1 hr per day</td>
<td>FM, ARAT, WMFT</td>
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</tr>
<tr>
<td>Triccas 2015</td>
<td>Subacute – Chronic</td>
<td>22</td>
<td>AA 35 cm²; 1 mA; 20 min; 9 days</td>
<td>Motor training; 1 hr per day</td>
<td>FM, ARAT, WMFT</td>
<td></td>
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<tr>
<td>Cunningham 2015</td>
<td>Chronic</td>
<td>12</td>
<td>AA 35 cm²; 1 mA; 30 min per stimulation</td>
<td>CIMT + therapy; 30 min / 2 day x 3 / week for 5 weeks</td>
<td>FM, 9-hole peg test, TMS</td>
<td>tDCS improved motor outcomes. Increased excitability in the contralesional hemisphere. Real stimulation plus therapy improved FM scores to a greater extent compared to therapy alone</td>
<td></td>
</tr>
<tr>
<td>Lee 2015</td>
<td>Chronic</td>
<td>24</td>
<td>AA 35 cm²; 1 mA; 20 min; 9 days</td>
<td>Motor training; 1 hr per day</td>
<td>FM, 9-hole peg test, TMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 2016</td>
<td>Subacute – Chronic</td>
<td>5</td>
<td>AA + CU 16 cm²; 1.5 mA; 30 min; 10 days</td>
<td>1 h OT/day; 10 days</td>
<td>FM, rsfMRI</td>
<td>FM scores improved. Increased connectivity between ipsilesional M1 and contralesional PMC</td>
<td></td>
</tr>
<tr>
<td>Mortensen 2016</td>
<td>Chronic</td>
<td>15</td>
<td>AA 35 cm²; 1.5 mA; 20; 5 days</td>
<td>OT; 30 min/day 5 days</td>
<td>JTT, grip strength</td>
<td>Both groups improved JTT. AA improved grip strength compared to sham (no longer present 1 wk post). Trend for JTT retention with AA</td>
<td></td>
</tr>
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larger, more homogeneous populations, evidence-based therapy, more integrated neurophysiological outcomes and, of course, studying the more plastic paediatric population.

We recently demonstrated the ability of tDCS to enhance motor learning in typically developing children. One previous study had demonstrated early evidence of safety, tolerability, and neurophysiological effects of brief tDCS applications to motor cortex in children. We conducted a 4 arm, blinded, sham-controlled trial of motor cortex tDCS to enhance motor learning in children aged 6–18 years. Subjects repeatedly performed a motor learning task (Purdue Pegboard) with their left hand over three days. They were randomly assigned to receive 20 min of contralateral anodal (1 mA), ipsilateral cathodal (1 or 2 mA) or sham tDCS during the first 20 min. Learning curves were strongly enhanced with active treatment with effects retained 6 weeks later and additional gains in untrained motor function of both hands (Fig. 4). We believe this provides important proof-of-principle evidence to advance further studies in hemiparetic CP and other disease populations.

Though there is much need for additional investigation, the most informed primary target in hemiparetic children with perinatal stroke currently is the contralesional M1. A cathodal approach is supported by the above evidence for tDCS effects in normal children and probable effect of the similar approach with inhibitory rTMS in the same population. Stimulation over intact (non-lesioned) brain also maximizes safety with more predictable distribution of tDCS currents compared to children with large arterial lesions. Methods should be based in the best accumulated evidence from previous studies of cathodal tDCS in addition to those cited above including adult motor learning and adult stroke rehabilitation and studies of electrode montages in stroke. Soft, replaceable 25 cm² electrodes would typically be placed on clean, dry areas of the scalp with the cathode placed over the non-lesioned M1. This location would ideally be individualized for each subject using TMS and/or task fMRI and targeted with neuronavigation. Consistent with previous tDCS stroke studies examining electrode placement, the reference electrode would be placed over the contralateral orbit. Using available, programmable, and current-controlled stimulators allows automatic ramp up slowly over 30 s to the treatment current, typically 1.0 mA tDCS or sham would usually be administered during the first 20–30 min of motor learning therapy and on a daily basis in a camp-based model. Experienced technicians should apply and monitor all systems, being on hand for immediate troubleshooting. Some tDCS systems can blind the administrator though it is only essential that clinicians administering therapy and those performing the outcome measures are blinded to treatment allocation.

We recently completed a phase 1/2, randomized, sham-controlled, double-blind, clinical trial to test whether the addition of tDCS to intensive motor therapy was associated with larger gains in clinical function. Participants completed a goal-directed, peer-supported after school camp model of motor learning therapy for 2 weeks, randomized to receive contralesional, cathodal tDCS (1 mA) or sham during the first 20 min of each day. Primary outcomes were the COPM (subjective) and AHA (objective) in addition to multiple safety and tolerability measures (see discussion below) measured out to 2 months post-intervention. The final results were presented at the 2016 International Stroke Conference in Los Angeles in February 2016 and is currently submitted for publication. In summary, interventions were well tolerated with no serious adverse events and all safety outcomes were satisfied. Significant tDCS effects were observed on COPM, but not AHA outcomes, suggesting possible benefit and providing important data for the execution of a larger, more definitive trial.

7. Systematic approach to clinical trial design: CONSORT

Any trial is only as good as the methods on which it rests. Thankfully, the importance of this fundamental concept has evolved over recent decades to carefully define the essential criteria of valid clinical trials and their reporting. The CONSORT (Consolidated Standards of Reporting Trials) statement is an evidence-based minimum set of standards for the reporting of randomized clinical trials. First initiated in 1996, the current version was last updated in 2010 and the most up to date version including recent modifications are available online. These include a 25 item checklist as well as a template flow diagram to account for participant movement through a trial.

An accompanying “explanation and elaboration” statement further defines each element and is available in multiple formats. Multiple extensions have also been developed to address designs beyond simple two group parallel designs such as cluster, non-inferiority, and pragmatic trials.

Use of the CONSORT guidelines has been associated with improved reporting of clinical trials. The website receives >17,000 hits per month. More importantly, over 600 journals have endorsed the CONSORT guidelines. While the primary motive for applying the CONSORT guidelines should be the best possible trial, it is fair to say that no future clinical trial will likely be published in any reputable journal without careful adherence. It is therefore reasonable to suggest that application of the CONSORT guidelines is both an extremely helpful and scientifically essential process in the design, execution, and reporting of any clinical trial. With this in mind, the outline of the guidelines will be applied below to review several essential elements of trial design as they relate to non-invasive brain stimulation trials in children. Outcome measures, the largest single issue, are discussed separately following this.

7.1. Populations

Where participant populations exist and how they are accessed for recruitment will primarily depend on the inclusion and exclusion criteria (discussed next). However, before these criteria are applied, the sample to be screened should be carefully selected to represent, as best as possible, the population of interest as a whole. Reductions from the true population toward the sample studied will inevitably introduce selection and other biases, the number and calibre of which decrease the translatability of any ultimate findings proportionately. Therefore, the optimal starting point is a large, complete, population-based sample of subjects with the condition of interest. As mentioned elsewhere, disease-specificity
will be a major determinant of this population. For example, from a population-based sample of cerebral palsy (something already difficult to find), perhaps 30% of these will be hemi-paretic and perhaps 75% of these will have confirmed perinatal stroke as the cause.

We began building the Alberta Perinatal Stroke Project (APSP) in 2007. This is a large population-based cohort of MRI-confirmed perinatal stroke consented to research now numbering nearly 800 subjects all living within the Canadian province of Alberta (population of ~4.2 million). This required an exhaustive review of over 80 ICD codes, 6000 medical charts, structured imaging review, patient contact and in person clinic assessments. The effort took over 7 years and is still ongoing.

The yield for clinical trials however was immense, providing a large unbiased sample from which candidates could be randomly recruited, optimizing translatability to the disease population as a whole. As outlined in the following sections on selection criteria and recruitment, this apparently very large number shrinks rapidly as these realities are introduced, further biasing the sample along the way.

7.2. Selection criteria

Further reduction of the eligible population for recruitment will occur with application of inclusion and exclusion criteria. Their selection must rest on the primary research question...
being asked; if this has to be compromised by changing criteria to suit other needs, the question should instead be changed. Once true to the primary question, additional issues of confounders, known response predictors, clinical realities (i.e. minimum function levels), clinical significance or need (i.e. maximal function levels), safety, and ability to comply must be considered. Criteria should be strictly quantified or qualified according to established metrics when possible.

The following provides an example of potentially relevant inclusion and exclusion criteria for a combined intensive motor learning and neurostimulation trial in hemiparetic CP.

7.2.1. **Inclusion criteria**

1. Symptomatic hemiparetic CP (Paediatric Stroke Outcome Measure (PSOM) > 0.5) AND Manual Abilities Classification System (MACS) grade I–IV AND child/parent perceived limitations in function
2. Clinical and MRI-confirmed perinatal stroke syndrome (NAIS, APPIS, PVI)
3. Active wrist extension >20°, finger extension >10°
4. Can lift the affected arm 15 cm above a table surface and grasp light objects
5. Term birth (>36 weeks) and current age 5–18 years
6. Informed consent/assent

7.2.2. **Exclusion criteria**

1. Other neurological disorder not related to perinatal stroke
2. Multifocal stroke
3. Severe hemiparesis (no voluntary contraction in paretic hand, MACS level V)
4. Severe spasticity in the affected limb (Modified Ashworth Scale >3)
5. Severe developmental delay or other inability to comply with study protocol
6. Unstable epilepsy (>1 seizure/month or >2 medication changes last 6 months)
7. Any TMS or MRI contraindication including implanted electronic devices
8. Botox, orthopaedic surgery, or other invasive mechanical therapy in past 6 months
9. Constraint, brain stimulation or other modulatory therapy in past 6 months

7.3. **Randomization**

Methods for randomization within clinical trials are complex and beyond the scope of this discussion. However, several fundamental issues to be considered relate predominantly to trial design and _a priori_ knowledge of response predictors and other potential confounders. Options including block or minimized randomization may help ensure balance of treatment allocation across subgroups of patients. Such subgroups may be easily defined (e.g. site A versus site B) or more complicated such as predefined factors known or highly suspected to be associated with the outcomes of interest or potential response to treatment. Examples might include factors such as age, level of baseline disability, or corticospinal tract arrangement. However, it should be emphasized that the relationship of these factors to the ability to respond to an intervention are incompletely, if at all, understood. Therefore, despite these specific considerations, it should be remembered that simple randomization should usually correct for such differences across treatment groups.

Most forms of randomization can be performed simply using patient codes and computer-based or online software administered by an unbiased study member such as the statistician. Concealment of randomization must be assured and multiple means are available. Development, storage, and breaking of codes by an unbiased third party may be reasonable. Treatment administrators can sometimes be automatically blinded, such as modern, programmable tDCS systems. Stimulation trials in children are likely moving toward multi-centre studies, introducing additional considerations. Randomization in permuted blocks, with the number of blocks matching the number of participating sites, may facilitate even distribution within sites. Multi-site trials on the other hand, may require a central randomization and treatment allocation process. Expertise from experienced clinical trialists and statisticians may be particularly helpful.

7.4. **Recruitment**

Failure to recruit complete samples on time is one of the most common reasons for trials to be delayed or not completed at all. Estimates of attainable sample sizes must be realistic (i.e. pessimistic). Hard numbers from established populations are required rather than blind estimates of prevalence based on published epidemiological data. What may appear as large, easily adequate number of potential subjects often reduces dramatically when realistic limitations are estimated. Examples include presence of exclusion criteria, inability to confirm all inclusion criteria, geographical factors, failure to recruit rates, and attrition with drop-outs possible at all stages (who must be included within intention to treat analyses if occurs following randomization).

7.5. **Informed consent and assent**

Consenting children and parents to novel, experimental trials of brain stimulation requires special attention. Potential benefits may be easily over-estimated by families of disabled children due to lack of alternative therapies, being “impressed” by technology, or other reasons. Risk must also be fairly disclosed based on best available evidence. Our lab has completed nearly 3 million stimulations on over 250 children with many conditions without serious adverse event. This provides direct evidence to families of minimal risk they can trust however such examples are not always available. Theoretical risks must be presented in context with estimates of relative risk and potential harm. An ability to understand randomization may be difficult to communicate and may be forgotten months later when final results are shared with families. Both parents and children, in our experience, may sometimes harbour feelings of disappointment or even mistrust when discovering they were in the sham group, even when they may have made substantial clinical gains. Honest,
7.6. Structure and flow

Structuring a complex, multifaceted intervention with numerous requirements for space, infrastructure, and highly qualified personnel requires organized structure. An example of the sequence, timeline and flow of our recently completed controlled trial of tDCS in school-aged children is shown in Fig. 2. Factors considered include family convenience where timing of drop offs and pick-ups, time of year (school year versus summer), and extracurricular activities may affect compliance and participation. Including unique activities may diversify therapy while optimizing fun for participants. Examples in our experience include virtual reality, cooking, therapeutic arts, horticultural therapy, and video gaming (e.g. rockband). Balancing focused motor training with more general and group activities as well as breaks and relaxation can be challenging. It is essential to include input from experts in paediatric therapy, child life, and subjects and their families for optimal planning.

7.7. Sham-control and blinding

Effective sham techniques are well established for non-invasive stimulation methods. For rTMS, this includes altering coil direction or use of commercially available sham coils. For tDCS, devices can often be ramped on for all subjects to produce the typically transient scalp sensations experienced, and then ramped off for the sham group. Such shamming has been proven effective,\textsuperscript{178} including in children.\textsuperscript{172,190} Cross-over design trials carry a risk of subjects detecting differences when they switch groups and interventions in naïve subjects only avoid this potential problem. Ideally, all investigators, those administering treatments, outcome assessors, parents and children remain blinded. Those administering tDCS may not be if they are otherwise separated from the outcome measures and therapy. Modern tDCS systems can also be programmed to randomize and administer accordingly, allowing the administrator to remain blinded.

7.8. Analysis and sample size

Statistical analysis will of course depend on the research questions to be addressed. In most circumstances, analysis will be intention to treat, accounting for all subjects randomized whether they complete the trial or not. Additional per protocol analyses may be performed and reported but this is not usually done in isolation. Collaborator expertise in clinical trials and biostatistical methods are an essential requirement. Variables for calculation of sample size should be extrapolated from the most relevant literature. Estimates are typically based on application of the first order analysis method to the main hypothesis using the primary outcome. Estimated samples should be comparable or proportional to previous trials in similar populations.

All studies need to be registered prior to consent of the first patient (www.clinicaltrials.gov).

8. Outcome measures

Selection of outcome measures is likely one of the most essential components of clinical trial design. Standardized, unbiased administration and interpretation by qualified experts blinded to treatment allocation and other clinical information is required but often challenging. Additional issues specific to considering neurostimulation interventions in children include a relative paucity of validated measures, heterogeneous populations (e.g. CP versus hemiparetic CP versus perinatal stroke hemiparesis), and variable effects of age and developmental level to name just a few. However, these limitations are being overcome through a variety of creative means to facilitate evaluation of such interventions. Measures used in similar previous trials should be considered in anticipation of comparability and eventual pooling of data in meta-analyses. At the same time, careful review of how well certain measures were able to demonstrate change (or not) and other limitations in those same trials may be good reasons to consider additional or alternative outcomes. Outcome measures can be considered under headings of clinical/functional, safety, and neurophysiological.

8.1. Clinical outcomes: motor function

A rigorous, evidence-based approach to clinical motor outcome selection should be adopted. Testing should be performed by a team of experienced experts that may include paediatric occupational and physical therapists, developmental paediatricians, paediatric neurologists and physiatrists, and clinical trialists. More specific outcomes may require additional expertise such as child psychology researchers when considering psychosocial and quality of life outcomes. Multidimensional evaluations should consider the body structure and function, activity and participation domains of the WHO International Classification of Functioning, Disability and Health (ICF), considering both unimanual and bimanual performance.\textsuperscript{191} Tools with established clinimetric properties in the population of interest (i.e. hemiparetic CP) are selected to evaluate diverse upper extremity functions relevant to daily living in children.\textsuperscript{198,199} Measures need to be both child and family friendly including sensitivity to time and fatigue. Measurement of both uni- and bi-lateral function of both limbs are required for normative data, evaluation of different clinical functions, and safety (including screening for changes in unaffected hand function). Testing should be video-taped for quality assurance, inter-rater validation, and additional offline analysis. Motor outcomes are measured at baseline, and 1 week, 2 months post-intervention.

With these principles in mind, the following three potential primary outcome measures might be considered in a clinical trial of intensive motor learning therapy combined with non-invasive brain stimulation in hemiparetic children. An additional list of possible secondary outcomes and their supporting evidence and attributes are summarized in Table 2.
Table 2 – Examples of potential functional outcome measures for clinical trials of neuromodulation in hemiparetic CP.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Target</th>
<th>Application and evidence-base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Occupational Performance Measure (COPM)</td>
<td>Individual goals for therapy</td>
<td>Individualized, family-centred tool identified child and family-perceived difficulties and personal improvement goals for self-care, productivity (school), and activities. The same experienced OT screened potential goals with child and parents with consensus defining those goals that were both functionally relevant and reasonably achievable. Scaled scores for performance and satisfaction of each goal were obtained (1 lowest, 10 highest). Such subjective, patient-centred measures are increasingly considered essential in paediatric hemiparetic CP trials. The COPM is validated for paediatric hemiparetic CP trials across our age range. Sensitivity to change has been established with an increase in COPM scores of ≥2 units considered clinically significant.</td>
</tr>
<tr>
<td>Assisting Hand Assessment (AHA)</td>
<td>Bimanual function</td>
<td>The AHA is an established evidence-based standard for the objective quantification of bilateral hand function in children with hemiparetic CP. Certified occupational therapists administer a structured, play-based assessment of spontaneous bimanual hand use followed by itemized scoring of the videotaped session. This Rasch-built evaluation carries the strongest evidence of inter-rater, intra-rater, and test-retest reliabilities, test-validity, and responsiveness to change for bimanual tasks in hemiparetic CP children within our age range. Sensitivity to change and excellent clinimetric properties have been established in paediatric hemiparetic CP trials. Consistent with validated methods, AHA scores are expressed as logit units with an increase of ≥5 units considered clinically significant.</td>
</tr>
<tr>
<td>Melbourne Assessment of Unilateral Upper Limb Function (MA)</td>
<td>Unimanual function</td>
<td>The MA is a validated, criterion-referenced functional measure designed to detect change in hemiparetic children. Trained therapists evaluate upper extremity motor tasks with performance ranked for each creating a total maximal score of 122 points (reported as percentage). Validation studies have correlated MA with clinically relevant functional outcomes in school-aged children.</td>
</tr>
<tr>
<td>Jebsen Taylor Test of Hand Function (JTTHF)</td>
<td>Unimanual function</td>
<td>1. Standardized timed test of unimanual upper extremity functional activities evaluating efficiency of movement. Important for comparability as the most common outcome measure used in adult stroke tDCS clinical trials and recent paediatric CP studies.</td>
</tr>
<tr>
<td>AbiHAND</td>
<td>Manual function</td>
<td>Designed to assess manual function in children with cerebral palsy, the AbiHAND scores 21 common manual activities in children at 3 levels of difficulty with summary logit unit scores. This measure is not specific to hemiparetic children but has been used in other paediatric CIMT trials.</td>
</tr>
<tr>
<td>Grip and pinch strength (GS, PS)</td>
<td>Motor function</td>
<td>GS is a simple, quick measure of hand motor function quantifiable with a dynamometer employed in many paediatric hemiparetic CP and adult rTMS stroke trials. Unaffected hand GS and PS are also potential safety outcomes.</td>
</tr>
<tr>
<td>Box and blocks (BB)</td>
<td>Dexterity</td>
<td>This test of unimanual dexterity will be applied on both sides as in previously reported paediatric CIMT trials. Assessment of the unaffected limb provides a safety measure (described above).</td>
</tr>
<tr>
<td>Purdue pegboard test (PPT)</td>
<td>Dexterity</td>
<td>2. Performed bilaterally to measure manual dexterity and is commonly used in paediatric CIMT studies, and was the primary outcome in our healthy tDCS motor learning trial in children.</td>
</tr>
<tr>
<td>PedsQL Cerebral Palsy Module (3.0)</td>
<td>Quality of Life</td>
<td>Condition specific and validated, age-adjusted child and parental reports assessed domains of daily activities, school activities, movement/balance, pain/hurt, fatigue, eating activities, and speech/communication.</td>
</tr>
<tr>
<td>APSP Parental Outcome Measure (POM)</td>
<td>Parental psychology</td>
<td>Measures adverse parental psychological outcomes in parents of children with perinatal stroke including unique symptoms of maternal guilt and blame.</td>
</tr>
</tbody>
</table>
8.1.1. Primary objective motor outcome: Assisting Hand Assessment (AHA)

This is currently the established standard for the objective quantification of bilateral hand function in children with hemiparetic CP. A Rasch-built evaluation, the AHA carries the strongest evidence of inter-rater, intra-rater, and test-retest reliabilities, test-validity, and responsiveness to change for bimanual tasks in hemiparetic school-aged children. Sensitivity to change and excellent clinimetric properties have been established in multiple pediatric HCP clinical trials. One potential limitation of the AHA is a drop in score when new unimanual functions have not yet been incorporated into the bimanual tasks being measured (i.e. scores may drop despite new function). Our trained therapists have successfully executed >200 AHA measurements within multiple clinical trials with excellent compliance and robust data.

8.1.2. Primary subjective motor outcome: Canadian occupational performance measure (COPM)

Subjective outcome measures are now considered a valid, potentially essential outcome measure in rehabilitation trials including children with hemiparetic CP. It could be argued that any gains shown in objective tests of motor function (e.g. strength, dexterity) are meaningless if the patients themselves have not perceived the achievement of a personal goal or some other personal satisfaction. For these reasons, individualized, patient-centered, goal directed tools such as the COPM have been developed and validated. Applied by an experienced pediatric OT in combination with child and parents, the COPM can identify child and family-perceived difficulties in categories of self-care, productivity (school), and activities. Validated for both school-aged children and pediatric hemiparetic CP trials, the COPM has been a robust measure in our previous perinatal stroke trials. We have also recently characterized how COPM goals are set in this population and their relationship to success in such interventional trials (Haspels et al., 2016, unpublished data).

8.1.3. Novel “real-life, continuous” motor outcome: actigraphic symmetry index (ASI)

No existing motor outcome measure can quantify continuous use of the upper extremities during the normal activities of real life. We recently proposed to overcome this limitation using actigraphy. Lightweight wrist accelerometers can constantly measure and store subtle movements (e.g. fitbit). Such systems can also track movements in disabled persons including those with CP. In upcoming trials, we will use the Actiwatch2 system to record mean movements every 15 seconds for 48 hour epochs of time (baseline, 2 months, 6 months) as well as continuously during the 2 week intervention phase. Importantly, we will do this bilaterally (2 watches), allowing the generation of a symmetry index between the affected and unaffected limbs. Our preliminary data has established the feasibility and accuracy of these methods in school-aged children (Cole et al., unpublished data).

Many additional clinical outcome measures can be considered depending on the nature of the trial. Examples, including their supporting evidence and primary targets, are summarized in Table 2.

8.2. Safety outcomes

With limited non-invasive neuromodulation data in the developing brain, careful and complete application of safety outcomes is paramount within clinical trials. Adult guidelines and safety reviews are available for both TMS and tDCS, and are certainly applicable. However, issues unique to children need to be screened for and rates of tolerability and potential adverse events documented. Safety issues should be identified a priori by experienced investigators but also at arms-length by a data safety and monitoring board (DSMB). Interim safety analyses may be incorporated into trial design at set time points (e.g. after certain numbers of subjects have completed outcomes). These analyses, as well as any serious adverse events, should be reviewed by the DSMB and institutional ethics boards requirements according to established, pre-defined protocols.

Safety can be considered under the following headings.

8.2.1. Serious adverse events

Typical definitions of SAE are adverse events or reactions that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Fortunately, SAE reports in non-invasive brain stimulation have been exceedingly rare across decades of use.

8.2.2. Function-specific adverse effects

Unique undesired outcomes may occur in specific studies. In the case of modulation trials for hemiparetic CP, one example is provided by the known control of both upper extremities by the non-lesioned hemisphere. Subsequently, inhibitory stimulation of the contralesional motor cortex might include theoretical consideration of reducing hand function in the unaffected hand or in the target affected hand, particularly in those with prominent ipsilateral corticospinal arrangements. Therefore, primary safety outcomes in our brain stimulation trials have included regular measures of both affected and unaffected hand function across time points for each subject and within interim safety analyses.
8.2.3. Side effects

Any intervention capable of having biological effects must also have the risk of side effects. Extrapolating from the much larger volume of evidence from the adult brain stimulation world and published guidelines, a reasonable list of side effects to be specifically screened for can be generated. These include feelings of headache or neck pain with TMS with the addition of itching or burning sensations for tDCS. However, symptoms specific to young age groups may exist, such as TMS-induced vasovagal syncope in adolescents. Each anticipated subjective symptom can be screened for and quantified including scale severity, duration, need for treatment, etc using a simple form. Screening and documentation should be repeated over time to assess for persistence or tolerance.

8.2.4. Tolerability

A standardized safety and tolerability evaluation for TMS in children has been developed and is easily adapted for different population and modalities including tDCS. Subjects are asked to rank order their stimulation experience amongst 7 other common childhood experiences.

Optimizing safety requires attention to each of the above issues. Brain stimulation studies in children should be performed by experienced personnel in a secure environment. Immediate access to medical care should be available in the unlikely occurrence of a serious adverse event. Written standardized operating procedures, for both experimental methods and handling adverse events, should be implemented and staff tested for their familiarity with these.

Our single centre experience has administered nearly 3 million stimulations to over 280 children in the past 8 years. Ages ranged from 8 months to 19 years (median 11.2) with the vast majority being school-aged. The most common conditions were perinatal stroke/cerebral palsy (70), mild traumatic brain injury (TBI, 68), or typically developing (53). Multi-disciplinary neurophysiological studies included single- and paired-pulse TMS methods. Therapeutic clinical trials used repetitive TMS (rTMS) and anodal/cathodal motor cortex tDCS. Prospectively collected safety and tolerability data on all subjects included the paediatric TMS safety and tolerability measure, child and parental interviews, and data safety and monitoring boards. There were no serious adverse events. Tolerability between TMS (402,680 stimulations) and rTMS (2.1 million stimulations) was comparable and rated similar to a long car ride. Although >100 had brain injuries and/or epilepsy, no seizures occurred. Headache following a TMS neurophysiology protocol was more common in perinatal stroke (40%) than typically developing (13%) participants but was mild and self-limiting. Mild neck pain with was relatively common but comparable between perinatal stroke (22%), depression (19%), and TBI (19%). Tolerability improved over time with rates of headache, neck pain, and unpleasant tingling decreasing by >50% at repeat testing. Of 51 children receiving tDCS, scalp itching in 55% was mild, transient, and comparable to sham with no drop-outs. Neither low frequency rTMS or cathodal tDCS of the non-lesioned hemisphere decreased function of either hand in children with hemiparetic cerebral palsy. We believe this data supports that brain stimulation is safe and well tolerated in children.

9. Neurophysiological outcomes

Advanced neurotechnologies have greatly advanced the ability to understand developmental plasticity in real patients. This includes baseline measures to evaluate natural process and how they relate to function but also the opportunity to explore the potential mechanisms of intervention-induced change. Combining modern technologies allows the comprehensive, integrated study of brain structure and function personalized to each individual. Clinically relevant examples of such integration are increasingly available in adults but awaiting full exploration in children. Summarized here are leading applications of single- and paired-pulse TMS, imaging including task and resting state fMRI and diffusion tensor imaging (DTI), and robotics.

9.1. Transcranial magnetic stimulation (TMS)

First described in 1985, most TMS studies are published since 2008 but only <3% include children. Focused magnetic fields applied across neuronal membranes result in focal depolarisations of human cortex according to Faraday’s Law. With narrow spatial resolution, TMS can affect discrete functional areas, offering non-invasive, painless mapping of motor systems. Tools relevant to the current study include “single-pulse” measurements such as motor evoked potentials (MEP) which quantify motor pathway neurophysiology from cortex to muscle. Motor thresholds and stimulus–response curves reflect corticospinal excitability. Paired-pulse TMS employs multiple stimuli to elucidate interactions between different brain areas. TMS is safe and well tolerated in children supported by animal studies and published guidelines. Application is safe in adult stroke and supported by our safety work in children with stroke. TMS-related seizures have not been described in children including administration over seizure foci. Modern technologies include single pulse systems for excitation and pathways as well as paired-pulse methods capable of probing cortical excitatory, inhibitory, and other physiological functions. Neuronavigation systems such asBrainsight (Rogue Research, Montreal) allow real time co-registration of coil location with individual subject MRI in three dimensions, including overlay of functional imaging targets. We have successfully demonstrated each of these methods in children with stroke. Single pulse TMS can determine bilateral M1 excitability. Motor evoked potentials are recorded from hand muscle, often the first dorsal interosseous (FDI), bilaterally. The motor “hotspot” is defined over M1 as the area producing consistent, high amplitude MEP. Resting motor threshold (RMT) is then defined as the
stimulator intensity required to produce MEP $\geq 50 \mu$V in 5/10 trials. Our studies suggest stroke side MEP are obtainable in $>80\%$ of subjects. Activated motor thresholds are also obtained during $-20\%$ of maximal FDI activation via visual feedback. Motor maps can also be created in the lesioned and unlesioned hemisphere. We recently added a TMS Robotic system (Axilum, Strasbourg) that should greatly facilitate execution of such outcomes.

Additional potential TMS neurophysiological outcomes include: (1) Stimulus response curves (rest and active). Bilateral M1 excitability is quantified by measuring MEP amplitudes across 5 escalating stimulus intensities such as 100/110/120/130/140/150% of RMT. (2) Interhemispheric Inhibition (IHI). Bidirectional IHI (lesioned to unlesioned hemisphere and vice-versa) applies stimuli to both M1 in quick succession with methods described elsewhere. Paired-pulse TMS applies a suprathreshold conditioning stimulus (CS) contralaterally immediately prior to a test stimulus (TS) with interstimulus intervals of 10 and 40 ms. The decrease in TS MEP quantifies IHI. (3) Short interval intracortical inhibition (SICI). M1 SICI can be determined according to established paired-pulse methods. For example, after suprathreshold CS, SICI effects are typically seen with an interstimulus interval of 2 ms. These and other TMS measures of cortical neurophysiology can define baseline function as well as changes occurring secondary to interventions.

9.2. Functional MR (fMRI) and the resting state (rsfMRI)

Functional MRI extrapolates regional brain activity from changes in blood oxygen-dependent signal. Two fMRI modalities have provided valuable insight to motor physiology, development, and stroke recovery. Task-dependent fMRI compares regional activity between on and off states during performed motor tasks. Task fMRI has established fundamental principles of development and stroke recovery including the roles of each hemisphere (above). Small hemiparetic CP studies have demonstrated similar utility and support our model. However, task fMRI only studies individual brain areas rather than the integrated neural networks.

“A connectivity-based system perspective is much closer to the neurobiology underlying brain physiology compared to analyzing anatomically segregated regions (i.e. traditional fMRI).” Resting state fMRI (rsfMRI) is a recent advance that facilitates such network analysis. Simple acquisition of fMRI data during patient rest can be acquired by both exploratory and hypothesis-driven methods to create models of functional and effective network connectivity. Such rsfMRI approaches now provide invaluable insight to brain plasticity mechanisms in adult stroke. Resting state motor networks are measurable in young children but are relatively unstudied in perinatal stroke. The stark contrast provided by arterial (cortical lesions at term) and PVI (preterm, subcortical) creates an ideal human model to explore motor network development after perinatal brain injury. Furthermore, changes in functional networks likely represent an essential measure of intervention-induced plasticity. Recently, such approaches have been validated in adults where change induced by brain stimulation interventions may be demonstrated using rsfMRI.

9.3. Diffusion tensor imaging (DTI)

Diffusion MRI acquires microscopic information on structural brain connections. DTI measures preferential water molecule diffusion (Brownian motion) along axonal axes, providing unique structural and physiological information in the developing and diseased brain. DTI utility has been demonstrated across numerous childhood neurological disorders and can be synergistically integrated with fMRI and TMS to create comprehensive, in vivo models of brain structure and function. Perinatal stroke DTI studies are few though CP applications support feasibility. We recently demonstrated our ability to evaluate corticospinal tract integrity in perinatal stroke using DTI.

9.4. Robotics

Robots have further advanced the ability to measure complex clinical function in disabled patients. Robotic technologies such as the KINARM (Kinesiological Instrument for Normal and Altered Reaching Movement) can assess limb movements at the shoulder and elbow. Unique advantages complimentary to the above modalities are conferred. For example, position sense is probably a major contributor to disability in hemiparetic patients. However, a lack of objective measures of such function has limited study. Using KINARM, the characteristics of position senses dysfunction are increasingly well characterized in adult stroke. We have shown that the same methods are well tolerated by children where a standardized, validated assessment of sensorimotor function can include two tasks that specifically target proprioception. Position sense can be measured using a position matching task; the robot moves the affected arm to random spatial locations and the subject then attempts to mirror match the positions with the unaffected arm. To measure kinaesthesia; the robot moves the affected arm. Subjects are required to move the good arm to match speed, amplitude and direction. Both tasks are completed first with vision occluded and again without the blindfold to determine their ability to compensate with vision. Using these methods, we recently demonstrated the common occurrence of such deficits in children with perinatal stroke and their association with clinical function. Such robotic outcomes will be available tool in identifying new modulation targets and assessing outcomes from the interventional trials at result.

10. Future directions

The translational pipeline from proof of principle through the phases of early stage clinical trials to the accumulation of multiple, positive, multicentre fully powered trials must be considered. The prolonged nature, and associated high costs, are likely comparable to drug development in some regards though potentially more economical. For example, rTMS for
adult major depression has driven the field of therapeutic non-invasive neuromodulation. Despite many positive randomized controlled trials spanning more than a decade, the intervention is only just now becoming an insured service in many developed countries. The extremely common occurrence, poor response rates to current medications, and disabling nature of major depression have likely driven this process relatively quickly. In comparison, treating different forms of cerebral palsy in children may not carry the same weight, further slowing the process. This should not discourage effort but is a considered reason to optimize the design, execution, and progress of early clinical trials.

The economics of such interventions in children have not been studied and remain difficult to estimate with such a limited number of trials to date. However, camp-based intensive motor learning is both a likely prerequisite for neuromodulation in children with motor disability as well as being an expensive, resource-intensive endeavour. Full day programs may be required to reach adequate dosing. Highly qualified personnel are many for such programs, including skilled therapists to both deliver treatment and administer outcomes. We have tried to mitigate some of these costs with after-school therapy programs and incorporating student therapists to administer therapy under the guidance of more experienced therapists. Home-based therapy programs are increasing in popularity for these reasons and may become feasible as portable, simple stimulation devices are developed. Such tDCT systems are already being designed including patient-friendly operation and ability for remote programming and monitoring by study investigators. However, home programs may risk removing the substantial psychosocial benefits young people may receive from participating in camp based programs. These issues will need to be carefully weighed in the design of future trials.

Neuromodulation trials in children with cerebral palsy bring the possibility of precision medicine to paediatric rehabilitation. While predictors of response to such interventions have not yet been well defined, there is little doubt that individual factors such as age, baseline disability, lesion type or location, and corticospinal tract arrangement likely play a role. A recent review suggested a possible systematic approach to classify hemiparetic children based on clinical (e.g. mirror movements), TMS (corticospinal tract orientation), and imaging (corticospinal tract integrity) variables. These are logical steps that are yet to be validated but carry the potential to bring personalized medicine to the rehabilitation of children with hemiparetic CP.

**Conflict of interest**

None.

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