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Reducing cortical inhibition: A conceptual hypothesis of dynamic recovery after perinatal stroke

Gabriel Augusto Castillo Castelblanco[1], **Robert Chen**[2,3,4]

Abstract

Introduction: The onset of perinatal stroke often goes unnoticed, and it is only recognized several months or even years later, typically as hemiparetic cerebral palsy. This delay makes it nearly impossible to conduct longitudinal studies from the time of injury, hindering the understanding of the underlying pathophysiological mechanisms and limiting the development of targeted therapeutic strategies.

Contents: This analysis supports the conceptual hypothesis that a reduction in cortical inhibition after perinatal stroke contributes to recovery and further suggests that this reduction may be induced by deafferentation. As muscle activity begins to recover, the degree of deafferentation also changes, leading to a dynamic and sequential modulation of cortical inhibition. This evolving inhibitory state influences the way in which the motor system reorganizes, ultimately shaping the three corticospinal patterns observed in patients with perinatal stroke. Based on this model, transcranial stimulation is discussed as a potential avenue for future research, given its capacity to reduce cortical inhibition.

Conclusion: It is proposed that recovery from perinatal stroke follows a dynamic and sequential process, which is represented by three corticospinal patterns. This conceptual framework opens up new avenues for future research, including the potential for personalized therapeutic strategies involving transcranial stimulation, tailored to each patient's unique corticospinal organization.

Keywords: Cerebral palsy, Stroke, Neural inhibition, Transcranial direct current stimulation, Transcranial magnetic stimulation, Pyramidal tracts, Motor evoked potentials.

Reducción de la Inhibición cortical: una hipótesis conceptual de recuperación dinámica tras el ACV perinatal

Resumen

Introducción: el inicio del ataque cerebrovascular (ACV) perinatal a menudo pasa desapercibido y solo se reconoce varios meses o incluso años después, típicamente en forma de parálisis cerebral hemiparética. Este retraso hace que sea casi imposible realizar estudios longitudinales desde el momento de la lesión, lo cual dificulta la comprensión de los mecanismos fisiopatológicos subyacentes y limita el desarrollo de estrategias terapéuticas dirigidas.

Contenidos: este análisis respalda la hipótesis conceptual de que una reducción de la inhibición cortical contribuye a la recuperación tras un ACV perinatal y sugiere, además, que dicha reducción podría ser inducida por la desaferentación. A medida que se inicia la recuperación de la actividad muscular, el grado de desaferentación también cambia, lo que conlleva una modulación dinámica y secuencial de la inhibición cortical. Este estado inhibitorio en evolución influye en la manera en que el sistema motor se reorganiza, dando lugar a los tres patrones corticoespinales observados en pacientes con ACV perinatal. Con base en este modelo dinámico de recuperación, se discute la estimulación transcraneal como una posible línea de investigación futura, aprovechando su capacidad para reducir la inhibición cortical.

Conclusión: este artículo propone que la recuperación tras un ACV perinatal sigue un proceso dinámico y secuencial representado por tres patrones corticoespinales. Esta perspectiva conceptual abre el camino para investigaciones futuras, incluyendo la posibilidad de estrategias terapéuticas personalizadas mediante estimulación transcraneal ajustadas a la organización corticoespinal del paciente.

Palabras clave: parálisis cerebral, accidente cerebrovascular, inhibición neural, estimulación transcraneal por corriente directa, estimulación magnética transcraneal, tractos piramidales, potenciales evocados motores.

1 Clínica Reina Sofía, Bogotá, Colombia
2 Krembil Research Institute, University Health Network, Toronto, ON, Canada.
3 Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, ON,] Canada.
4 Division of Neurology, University of Toronto. Toronto, ON, Canada.

Correspondence / Correspondencia:
Gabriel Augusto Castillo Castelblanco, Clínica Reina Sofía, Calle 127 # 20-56, Bogotá, Colombia.
E-mail: castilloneuro@yahoo.com

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Introduction

Perinatal stroke is the primary cause of hemiparetic cerebral palsy (HCP) (1), the most common type of cerebral palsy (2). Perinatal stroke, defined by the NICHD–NINDS consensus as cerebrovascular events occurring between 20 weeks of gestation and the 28th postnatal day (3), has consistently been referred to within this gestational–perinatal window in the literature (4). Unlike stroke in children and adults, in which the timing of the event is usually identifiable, perinatal stroke is often recognized only several months or even years after its onset (5). This delay in diagnosis presents a major scientific challenge, as it hinders longitudinal study of the recovery process from its earliest stages and limits the development of targeted therapeutic strategies.

A recent study demonstrated that in most patients with HCP, including children, adolescents, and young adults (7–22 years of age), corticospinal excitability related to the affected hand increased. This excitability was measured by motor evoked potential (MEP) amplitude. The increase occurred following the application of anodal transcranial direct current stimulation (a-tDCS) (6). The stimulation was applied to the affected hemisphere (AH) in some patients and to the unaffected hemisphere (UH) in others. Given that a-tDCS can reduce cortical inhibition (CI) (7), these results support the conceptual hypothesis that a reduction in CI could contribute to the recovery process in perinatal stroke (8). Additionally, the study suggests that both hemispheres participate in recovery, although neither of these interpretations was explicitly mentioned by the authors (6).

In perinatal stroke, patients with a prenatal injury tend to experience better outcomes than those with postnatal onset (9), and recovery potential decreases as the timing of injury during pregnancy approaches term (10). These findings are consistent with the well-established observation that children recover better than adults after stroke due to greater plasticity, suggesting that the earlier the stroke occurs, the greater the potential for recovery (11). Since lowering inhibitory tone enhances plasticity in the human motor cortex (12), and younger age is associated with lower levels of CI (13), we propose the conceptual hypothesis that recovery in perinatal stroke depends not only on the presence of this reduction but, more importantly, on its extent.

If these concepts are correct and given that both a-tDCS and high-frequency repetitive transcranial magnetic stimulation (rTMS) can reduce CI (7,14), these techniques may represent promising avenues for future therapeutic research as an adjunct to rehabilitation in children and adolescents with perinatal stroke. It is important to emphasize that these strategies are not considered interventions for neonates or infants, and evidence in very young children remains scarce.

The role of deafferentation in reducing cortical inhibition

Studies on animal models suggest that deafferentation due to limb amputation during the perinatal period may decrease the motor excitability threshold and increase the size of the motor representation area (15). Studies using transcranial magnetic stimulation have shown similar effects in adult humans who have undergone amputation, attributing them to a reduction in CI (16). Therefore, it is possible that during the perinatal period in humans, deafferentation may also lead to a decrease in CI.

Neuropathological studies of patients with perinatal brain injury, including those with cerebral palsy, have revealed a loss of corticopetal fibres, indicating a state of deafferentation (17). In adult stroke patients, afferent input plays a critical role in modulating motor cortex excitability (18). Similarly, deafferentation has been shown to reduce CI in both hemispheres in animal models of stroke (19). Since HCP is primarily caused by perinatal stroke (1), it is possible that deafferentation in these patients leads to a bilateral reduction in CI, although this remains to be confirmed.

Interestingly, deafferentation has also been explored as a therapeutic strategy. In chronic stroke patients, temporary deafferentation induced through regional anesthesia has led to a 'dramatic' motor improvement (20). However, despite level B evidence supporting this approach (21), its clinical application remains limited due to the complexity and discomfort associated with the procedure (22).

Patterns of corticospinal reorganization in perinatal stroke

In patients with perinatal stroke, transcranial magnetic stimulation can be used to assess both the ipsilateral corticospinal tract (iCST) and the contralateral corticospinal tract (cCST) (23). The activity along

each of these pathways is measured by recording the corresponding motor evoked potentials: the ipsilateral MEP (iMEP) and the contralateral MEP (cMEP), respectively (23). Based on the presence (+) or absence (−) of these MEPs in the affected hand, three corticospinal patterns have been identified in perinatal stroke (23): the first pattern, iMEP+, cMEP−, is observed in patients whose affected hand is exclusively innervated by the iCST of the UH (Figure 1). The second, or intermediate pattern, iMEP+, cMEP+, indicates corticospinal innervation of the affected hand from both hemispheres (Figure 1). The third pattern, iMEP−, cMEP+, is found in patients who control the affected hand solely through the cCST of the AH (Figure 1).

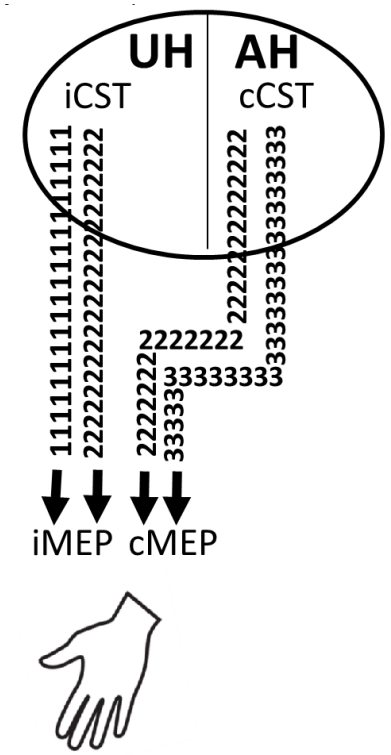

Figure 1. Corticospinal patterns in perinatal stroke

Note. The affected hand can be innervated by the ipsilateral tract (Line 1, Pattern 1), both hemispheres (Lines 2, Pattern 2), or the contralateral tract (Line 3, Pattern 3).

AH: Affected Hemisphere; CI: Cortical Inhibition; **cCST:** contralateral Corticospinal Tract; **iCST:** ipsilateral Corticospinal Tract; **cMEP:** contralateral Motor Evoked Potential; **iMEP: i**psilateral Motor Evoked Potential; **UH:** Unaffected Hemisphere.

Source: Own elaboration.

A corticospinal pattern-based model of recovery in perinatal stroke

Based on the above, we propose the following conceptual sequence for HCP recovery after perinatal stroke. The initial loss of muscle activity reduces afferent input to the brain. This decrease in proprioceptive information — or deafferentation —could affect both hemispheres (24), leading to a bilateral reduction in CI (Figure 2-A). Notably, an early bihemispheric reduction in CI has been observed in adult stroke patients (25–27).

Next, considering that in developing animals the reduction of CI can unmask corticospinal activity (28), it is plausible that the iCST of the UH is unmasked, and its activity is recorded as an iMEP. Meanwhile, the cMEP is not recorded due to the anatomical lesion in the AH. Thus, this stage of corticospinal reorganization after perinatal stroke would correspond to the iMEP+, cMEP− pattern (Figure 2-B). At this stage, patients exhibit the greatest deficits (23), which could be attributed to an insufficient reduction in CI, according to our previously mentioned hypothesis.

As time progresses, anatomical repair occurs in the AH, allowing the cCST to reinnervate the affected hand, which is reflected in the emergence of the cMEP. This stage matches pattern 2 (iMEP+, cMEP+) (Figure 2-C). The resulting dual innervation raises muscle activity in the affected hand, decreasing deafferentation and the degree of CI reduction. Consequently, the unmasking of the iCST ceases, leading to the disappearance of the iMEP. By this point, the recovery process has reached its final stage, where motor function in the affected hand is fully taken over by the restored cCST. This phase reflects pattern 3 (iMEP−, cMEP+) (Figure 2-D), which is observed in patients with better recovery (23) and who probably had a sufficient level of CI reduction. Thus, the reduction in CI could represent a transient, plasticity-related mechanism in perinatal stroke recovery. Notably, a return to normal CI levels has been well documented in adult patients after stroke recovery (27,29).

This proposed process for perinatal stroke recovery reinforces the concept that the relationship between motor function and intracortical excitability is dynamic—both in how it changes over time and how it reflects evolving cortical circuits—and critically dependent on the time elapsed since stroke onset (29).

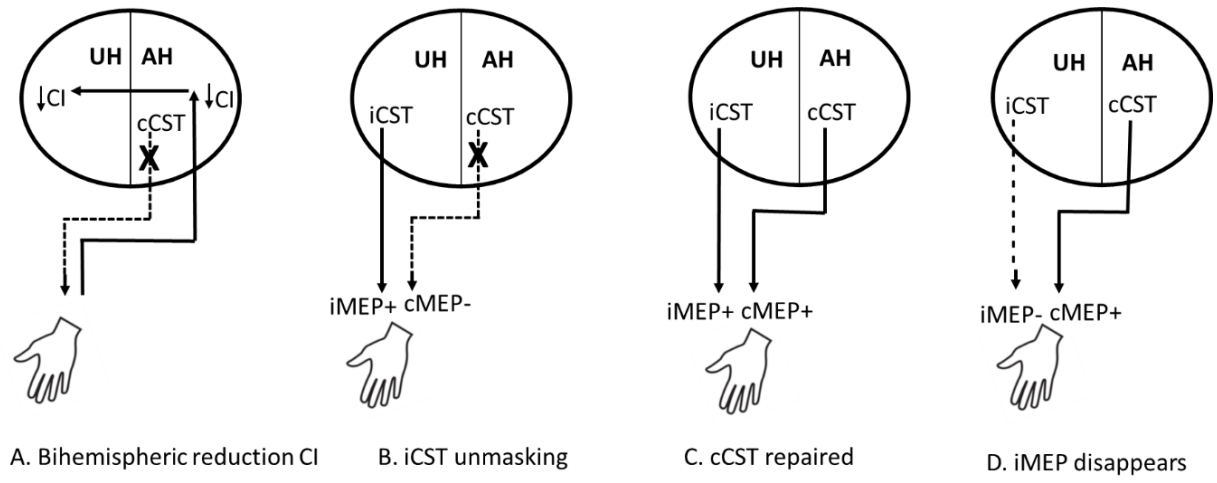

Figure 2. Proposed dynamic and sequential model of recovery after perinatal stroke

Note. (A) Deafferentation reduces bilateral cortical inhibition. **(B)** Ipsilateral innervation emerges: Pattern 1. **(C**) As anatomical repair progresses, bilateral innervation develops: Pattern 2. **(D)** Strength improvement reestablishes inhibition, the ipsilateral contribution subsides, and normal contralateral activity again assumes full control: Pattern 3.

AH: Affected Hemisphere; CI: Cortical Inhibition; **cCST:** contralateral Corticospinal Tract; **iCST: i**psilateral Corticospinal Tract; **cMEP:** contralateral Motor Evoked Potential; **iMEP:** ipsilateral Motor Evoked Potential; **UH:** Unaffected Hemisphere.

Source: Own elaboration.

Neurophysiological therapeutic strategies for perinatal stroke

Since corticospinal activity can be enhanced by reducing CI using a-tDCS or high-frequency rTMS (7,14), the proposed recovery model suggests that in future studies, these techniques can be tailored according to the patient's corticospinal pattern: in pattern 1, stimulation should target the UH; in pattern 2, both hemispheres; and in pattern 3, the AH.

As recovery progresses, changes in the corticospinal pattern are expected. Consequently, transcranial stimulation should be adjusted to align with the evolving reorganization, ensuring that only the regions requiring intervention are targeted.

In the study by Nemanich et al., the site of tDCS was determined solely based on the presence or absence of cMEP (6). Patients with cMEP+ received anodal tDCS over the AH, while those with cMEP- received it over the UH. In the cMEP- group, the authors confirmed the presence of iMEP, indicating a pattern of iMEP+, cMEP-, which corresponds to corticospinal pattern 1 and aligns with the proposed strategy of targeting the UH. Conversely, patients with cMEP+ could belong to either pattern 2 or pattern 3. For those with a potential pattern 3, stimulation over the AH is consistent with the proposed approach. Given that most patients in the Nemanich et al. study showed increased corticospinal activity in the affected hand (6), the findings support the proposed strategies for patterns 1 and 3. However, patients with a potential pattern 2 did not receive a stimulation protocol specifically tailored to their corticospinal organization.

Limitations and conclusions

This work should be understood as a conceptual hypothesis derived from existing literature and theoretical reasoning, rather than as a validated model. Several limitations should be noted. First, much of the supporting evidence originates from studies conducted on animal models or adults who have experienced a stroke or amputation. While these studies provide valuable insights, extrapolation them to perinatal stroke remains speculative and requires validation in pediatric populations. Secondly, this analysis does not address the epidemiological or population-level determinants that are essential

for contextualizing the clinical relevance of the proposed framework. Thirdly, the therapeutic implications discussed here, including the potential role of non-invasive brain stimulation, should be considered as suggestions for future research rather than as established clinical interventions. Finally, although it is proposed that corticospinal patterns may evolve dynamically with recovery, longitudinal studies are needed to confirm this sequence and to determine its variability across patients.

In summary, although this report is limited to a single conceptual framework, it provides a basis for future experimental validation of the proposed model of dynamic recovery in perinatal stroke.

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Ethical implications. As this study involved only literature review and interpretation, with no direct interventions, it does not raise any ethical concerns.

AI disclosure statement. The authors declare that no artificial intelligence tools were used in the preparation or writing of this manuscript.

Data availability statement. No data are available in a public repository. For inquiries regarding any information related to this article, please contact the corresponding author.

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