Rethinking interhemispheric imbalance as a target for neurorehabilitation

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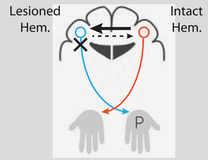
Introduction

What is the role of interhemispheric interactions in stroke recovery?

Interhemispheric competition model



The two hemispheres normally exert mutual inhibition in healthy individuals.

The intact hemisphere becomes overactive and inhibits the lesioned hemisphere. This extra suppression impedes recovery.

Evidence:

- BOLD activation in the contra-lesional hemisphere was found increased early after stroke, and correlated with poor outcome of hand gripping strength (Ward et al., 2003, a&b).
- Chronic stroke patients showed persistent interhemispheric inhibition (IHI) from the intact to the ipsilesional motor cortex prior to movement execution; and this increased premovement IHI was associated with poor muscle strength and finger tapping performance (Murase et al., 2004)

Two reasoning gaps:

1. While the heightened contra-lesional BOLD activity was found during the ***acute*** stage after stroke, the abnormal premovement IHI has only been shown in ***chronic*** patients.
   - Stinear et al. (2015) found that patients did not show impairment in ipsilateral silent period (ISP), an indirect measure of IHI over the first three months of recovery.
   - It is unclear if reduced premovement IHI is present early after stroke.
2. Reduced premovement IHI at chronic stage may not be causally related to the positive correlation between IHI and motor performance, as means and correlations are unrelated.

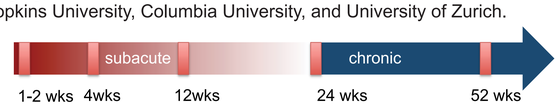
We investigated the evolution of interhemispheric interaction in the context of movement execution after stoke, and its role in motor recovery over one year period. We hypothesize that persistent premovement IHI may not be present during the acute and subacute stages after stroke.

Methods

Tracking motor recovery after stroke

In a multi-center study, we tracked motor recovery after stroke using clinical scales, psychophysics, functional and structural brain imaging, and noninvasive brain stimulation. Patients with first time ischemic stroke were enrolled from Johns Hopkins University, Columbia University, and University of Zurich.

Assessment time points:



Participants:

Twenty-two Patients: Age 57.5+/-16 years; Gender: 7 female, 15 male; Lesion side: 10 left, 12 right.

Eleven age-matched healthy controls: Age 69+/-9 years; Gender: 4 female, 7 male.

Overall our patient sample was mild to moderately impaired ($FMA_{initial}$ Mean = 41±22).

TMS procedures:

Resting motor threshold (rMT):

For both FDI muscles, minimal intensity evoked MEPs of ~50 μV (peak-to-peak amplitude) in the targeted muscle on five out of 10 consecutive trials.

Active cortical-spinal tract integrity (aCST):

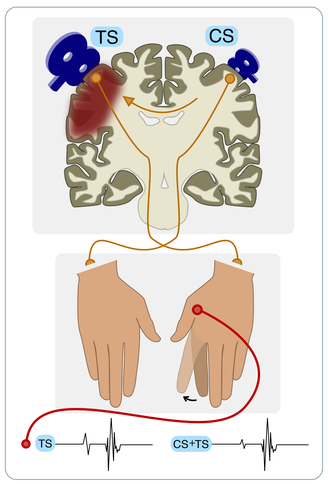
18 pulses with 100% MSO targeting both FDI muscles, when participants were contracting at 20% maximum voluntary contraction.

Interhemispheric inhibition (IHI):

IHI was assessed both *at rest*, and *prior to movement*.

A conditioning pulse (CS) was applied to the primary motor cortex (M1) of the unaffected (contralesional) hemisphere (right for controls); a test pulse (TS) was applied to the M1 of the lesioned hemisphere (left for controls).

On unconditioned (UC) trials, only a TS pulse was delivered. On conditioned (C) trials, both CS and TS pulses were delivered, with CS preceding TS by an inter-stimulus interval (ISI) of 10ms.

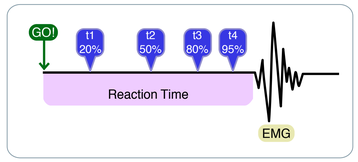


Assessment of premovement IHI

TMS pulses were delivered at four different timings according to each participant's reaction time (RT): 20, 50, 80, and 95%.

TS intensity: the minimum MSO that produced 0.5-1mV motor evoked potentials (MEP).

CS intensity: adjusted to the intensity that produce 50% reduction of the TS MEPs.



Behavioral Task:

Premovement IHI was assessed while participants performed a simple reaction task. Participant were asked to make a voluntary index finger abduction movement in response to the Go cue.

Reaction time (RT) was assessed before premovement IHI testing using the same task.

IHI measures:

$IHI = MEP_{C\_TS} / MEP_{UC\_TS}$

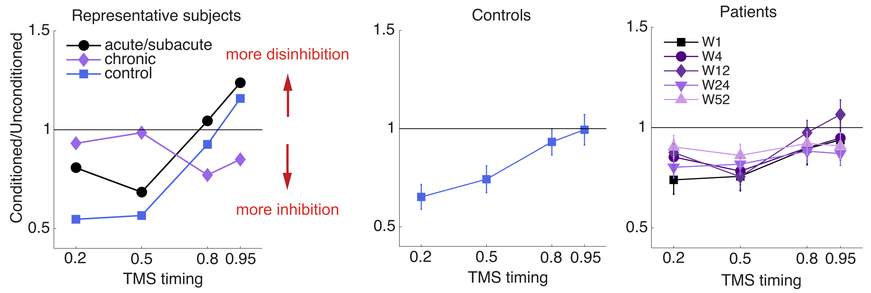
$IHI_{early\_epoch} = \text{mean}(IHI_{t1\text{-}t2})$

$IHI_{late\_epoch} = \text{mean}(IHI_{t3\text{-}t4})$

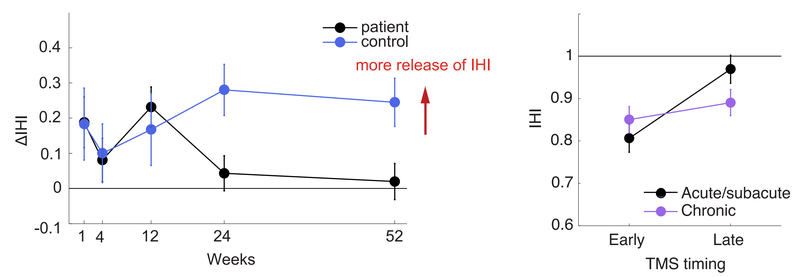
$\Delta IHI = IHI_{late\_epoch} - IHI_{early\_epoch}$

Results

Premovement IHI is normal in acute/subacute stages after stroke



Patients presented relatively normal levels of release of IHI during the acute/subacute period (W1-12), and persistant premovement IHI at chronic stages (W24-52). This is supported by a significant Week X Group interaction (χ^2 = 5.10, p = 0.02).

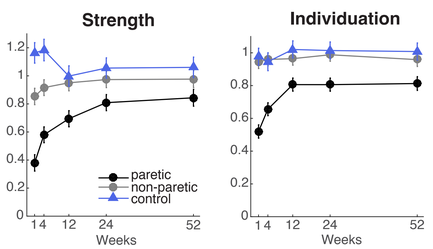


Abnormal premovement IHI at the chronic stage due to both reduced inhibition at early epoch of movement pareparation, and a reduction of release of this inhibition at late epochs (signification interaction of TMS-timing X stroke stage, χ^2 = 5.47, p = 0.019).

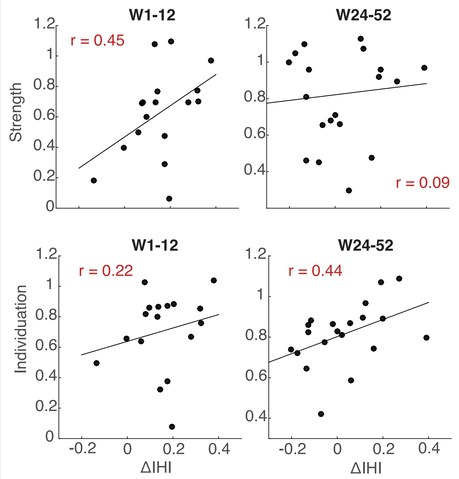
Hand function recovery plateaued after subacute stage

MVF: Patients depress each individual finger with maximum voluntary contraction.

Individuation: Patients depress each individual finger once, targeting at a particular force level (20, 40, 60, or 80% of MVF), while keeping other fingers immobile.



Release of premovement IHI correlates with hand function



Strength was correlated with *ΔIHI* at acute/subaccute stages (p = 0.067), but not chronic stage after stroke.

While this does not replicate Murase et al. (2004) finding, Strength measure in this study is quite different from what they used (MRC).

Individuation was correlated with *ΔIHI* at chronic (p = 0.05), but not acute/subacute stages after stroke.

This replicates Murase et al. (2004) finding in chronic patients.

Most strength and Individuation improved over the time period when the mean difference in ΔIHI was not different from controls. Nevertheless, similar correlations can be found at both acute/subacute and chronic stages.

There is no relationship between mean and correlations.

Release of premovement IHI is predictive of recovery

Cross-validated multiple regression showed that ΔIHI at acute/subacute stages added predictive power to the recovery of strength at chronic stage.

Dependent variable	Independent variables					Cross - validated	Simple regression
mean(W24 - 52)	mean(W1 - 12)	b0	b1	b2	N	R2	R2
Strength	Strength	0.37	0.65	-	15	0.38	0.57
	ΔIHI	0.65	1.44	-	15	0.44	0.56
	Strength + ΔIHI	0.38	0.44	0.96	15	0.67	0.76
Individuation	Individuation	0.30	0.65	-	15	0.14	0.35
	ΔIHI	0.78	0.26	-	15	-0.33	0.01
	Individuation + ΔIHI	0.20	0.86	-0.45	15	0.05	0.42

Discussion

We tracked patients' premovement IHI for one year following stroke. Premovement IHI was normal during the acute/subacute stages. The increased inhibition only emerged at the chronic stage.

Premovement IHI was correlated with finger strength at the acute/subacute, but not the chronic stage; and it was only correlated with finger individuation at the chronic stage.

The critical point is that the correlations between premovement IHI and stroke measures at any given time are dissociated from the longitudinal evolution of premovement IHI. This means that manipulating the latter does not necessarily change the former. Using brain stimulation to rebalance interhemispheric interaction after stroke needs to be rethought.

Premovement ihi might have some predictive value beyond the behavioral measures, but further investigation is needed to clarify the relationship between interhemispheric interaction and motor recovery after stroke.

References

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