Understanding Inter-hemispheric Inhibition in Stroke to Develop Severity-Specific Brain Stimulation

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Role of the Intact, Contralesional Motor Cortex

• In motor function of paretic upper limb
  • Widely debated
  • Inhibitory v.s. Supportive (compensatory)
Role of the Intact, Contralesional Motor Cortex

- Classical evidence
  - Contralesional motor cortices impose excessive inter-hemispheric inhibition (IHI) on the weak ipsilesional motor regions

Murase, Cohen et al. *Ann Neurol* 2004
Role of the Intact, Contralesional Motor Cortex

• More recent evidence
  • Contralesional motor cortices can make supportive contributions towards paretic limb movement

Single-pulse TMS interferes contralesional premotor cortex

Johansen-Berg et al. *PNAS* 2002
Bestmann et al. *J Neurosci* 2010
Mohapatra et al. *Neurosci Lett* 2017
Role of the Intact, Contralesional Motor Cortex

• A new theory: Bimodal-Balance Recovery Model
  • Based on the amount of ipsilesional reserve available to contribute to recovery
    • High reserve $\rightarrow$ Inhibitory
    • Low reserve $\rightarrow$ Supportive

Di Pino et al. *Nature Rev Neurol* 2014 (Adapted)
Questions

• Whether the role of intact, contralesional motor cortices indeed varies in a bimodal manner with severity of injury/deficit?
  • Identify a criterion

• How patients with different levels of severity respond to inhibitory or facilitatory brain stimulation over contralesional cortices?
Experiment I

• Purposes:
  • To characterize the relationship between
    • Contralesional influence (measured as IHI)
    • Severity of motor impairment and corticospinal damage
  • To identify a criterion of severity separating patients
Experiment I

- Subjects:
  - 24 patients
    - Age: 61.7 ± 8.9 years,
    - Chronic stroke (> 6 months)
  - Upper Extremity Fugl Meyer (UEFM) between 15-65
Experiment I – Methods & Procedure

- Inter-Hemispheric Inhibition (IHI):
  - Measured by ipsilateral silent period (iSP)

- Motor impairment: UEFM

- Corticospinal integrity:
  - Fractional Anisotropy asymmetry ($FA_{\text{Asymmetry}}$)

\[
FA_{\text{Asymmetry}} = \frac{FA_{\text{CONTRALESIONAL}} - FA_{\text{IPSICLESIONALL}}}{FA_{\text{CONTRALESIONAL}} + FA_{\text{IPSICLESIONALL}}}
\]
Experiment I – Results & Discussion

R² = 0.53, p = 0.0007

R² = 0.30, p = n.s.
Experiment II

• Purpose:
  • To investigate the responses of patients in different severity groups to inhibitory and facilitatory brain stimulation over contralesional motor cortices
    • Separate subjects into more-affected and less-affected groups (UEFM = 43)
Experiment II

• Subjects
  • 24 patients (age: 60 ± 2 years, chronic > 6 months);
    • More-affected: 12, less-affected: 12.
  • UEFM motor impairment score between 7-64
Experiment II – Methods

• Single-session crossover experiment: immediate effects
  • Repetitive TMS (rTMS) over contralesional motor cortices
  • Facilitatory (5Hz), inhibitory (1Hz), sham,

• Outcome measure: reaching time (RT)
  • Change in RT from sham

Sankarasubramanian et al. Clin Neurophys 2017
Experiment II – Results & Discussion
Discussion

- When brain stimulation is applied, severity of motor impairment should be considered

- Mechanisms of motor improvement in more-affected patients
  - Interhemispheric pathways
  - Ipsilateral pathways
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