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Inhibition versus facilitation of contralesional motor cortices in stroke: Deriving a model to tailor brain stimulation

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HIGHLIGHTS

- Mildly affected chronic stroke patients improved upon paretic upper limb reaching with standard inhibitory 1 Hz rTMS of contralesional motor cortex.
- Severely affected patients improved with a new method involving facilitatory 5 Hz rTMS of contralesional dorsal premotor cortex.
- A preliminary cut-off level of damage/impairment separated responders to each form of stimulation.

ABSTRACT

Objective: The standard approach to brain stimulation in stroke is based on the premise that ipsilesional M1 (iM1) is important for motor function of the paretic upper limb, while contralesional cortices compete with iM1. Therefore, the approach typically advocates facilitating iM1 and/or inhibiting contralesional M1 (cM1). But, this approach fails to elicit much improvement in severely affected patients, who on account of extensive damage to ipsilesional pathways, cannot rely on iM1. These patients are believed to instead rely on the undamaged cortices, especially the contralesional dorsal premotor cortex (cPMd), for support of function of the paretic limb. Here, we tested for the first time whether facilitation of cPMd could improve paretic limb function in severely affected patients, and if a cut-off could be identified to separate responders to cPMd from responders to the standard approach to stimulation.
Methods: In a randomized, sham-controlled crossover study, fifteen patients received the standard approach of stimulation involving inhibition of cM1 and a new approach involving facilitation of cPMd using repetitive transcranial magnetic stimulation (rTMS). Patients also received rTMS to control areas. At baseline, impairment [Upper Extremity Fugl-Meyer ($UEFM_{PROXIMAL}$, max = 36)] and damage to pathways [fractional anisotropy (FA)] was measured. We measured changes in time to perform proximal paretic limb reaching, and neurophysiology using TMS.
Results: Facilitation of cPMd generated more improvement in severely affected patients, who had experienced greater damage and impairment than a cut-off value of FA (0.5) and $UEFM_{PROXIMAL}$ (26–28). The standard approach instead generated more improvement in mildly affected patients. Responders to cPMd showed alleviation of interhemispheric competition imposed on iM1, while responders to the standard approach showed gains in ipsilesional excitability in association with improvement.
Conclusions: A preliminary cut-off level of severity separated responders for standard approach vs. facilitation of cPMd.

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Significance: Cut-offs identified here could help select candidates for tailored stimulation in future studies so patients in all ranges of severity could potentially achieve maximum benefit in function of the paretic upper limb.

1. Introduction

Stimulation of the brain is a well-accepted experimental technique for promoting recovery of the paretic upper limb after stroke. Based on the premise that ipsilesional primary motor cortex (iM1) is important for motor function (Nudo and Milliken, 1996) and contralesional motor cortices compete with iM1 to inhibit output devoted to the paretic upper limb (Murase et al., 2004), the standard approach involves facilitating iM1 and/or inhibiting the contralesional motor cortices (Fregni and Pascual-Leone, 2007; Di Lazzaro et al., 2013). However, this approach fails to generate much improvement in severely affected patients (Malcolm et al., 2007; Ackerley et al., 2010; Hesse et al., 2011; Talelli et al., 2012; Levy et al., 2015). These patients sustain extensive damage to ipsilesional pathways (Hedna et al., 2013), so emphasizing iM1 is less likely to affect function of the paretic upper limb (Nouri and Cramer, 2011; Levy et al., 2015; Simis et al., 2016). Instead, undamaged cortices, especially the contralesional dorsal premotor cortex (cPMd) may offer support (Johansen-Berg et al., 2002; Ackerley et al., 2010; Bradnam et al., 2012). Inhibition of cPMd (more than inhibition of any other contralesional region) impairs movement of the paretic limb in severely affected patients, suggesting that plasticity of cPMd makes causal contribution to their function of the paretic limb. cPMd is believed to support function by alleviating competition imposed on iM1 (Johansen-Berg et al., 2002; Bestmann et al., 2010; Chen and Schlaug, 2016; Mohapatra et al., 2016). Therefore, a more recent hypothesis suggests that undamaged areas like cPMd are key for recovery of severely affected patients, while iM1 is important only for mildly affected (Di Pino et al., 2014; Plow et al., 2016). This hypothesis is also referred to as the "bimodal hypothesis" of plasticity.

While it would seem logical to tailor stimulation according to the bimodal hypothesis of plasticity, several challenges remain. It is unclear what cut-off separates mildly affected patients from severely affected patients for application of tailored stimulation to iM1 and undamaged, contralesional cortices, respectively. Given that contralesional cortices have not been previously facilitated in humans, it is also unknown whether facilitating cPMd or facilitating other contralesional regions, like contralesional M1 (cM1) (Carmel et al., 2014; Buetefisch, 2015; Yao et al., 2015), would be more effective to support function in severely affected patients. Last, would stimulating contralesional cortices be even more effective than stimulating higher-order ipsilesional cortices, like ipsilesional PMd (iPMd) which may assume the role of iM1 in patients with severe damage (Carey et al., 2002; Ward et al., 2003a; Dancause and Nudo, 2011; Ward, 2011)?

To address these questions, we performed a series of randomized, sham-controlled, crossover experiments. In the main experiment, patients received stimulation based on a standard approach (inhibition of cM1), and stimulation that involved facilitation of cPMd, in line with the bimodal hypothesis. We measured change in time to perform proximal reaching at the paretic upper limb to index improvement in function (Harris-Love et al., 2011) and change in neurophysiology to index plasticity associated with stimulation. At baseline, we assessed impairment using a common clinical scale (Fugl-Meyer et al., 1975) and damage to pathways using diffusion tensor imaging (DTI) (Stinear et al., 2007) and transcranial magnetic stimulation (TMS) (Rossini et al., 1994). We hypothesized that as baseline damage/impairment would become severe, patients would fail to improve with the standard approach involving inhibition of cM1, and instead improve with stimulation facilitating cPMd. Since the relationship between damage/impairment and change in proximal reaching associated with both techniques would be opposite, we anticipated intersection of their regression curves would serve as the cut-off value of severity that separates patients responding to standard inhibition of cM1 from patients responding to facilitation of cPMd. We also anticipated that responders to standard cM1 inhibition technique would experience gains in ipsilesional output with improvements in proximal reaching, while responders to cPMd facilitation would show alleviation of competition imposed on iM1 from contralesional cortices.

In a separate experiment, a subset of patients with severe ipsilesional damage also received stimulation to facilitate cM1 in order to help understand whether stimulating cPMd or cM1 elicits more improvement in severely affected patients. We anticipated greater improvements with facilitation of cPMd, in association with greater reduction in competition imposed on iM1.

In another control experiment, patients additionally received stimulation of iPMd. We tested the hypothesis that as baseline damage/impairment would become severe, patients would fail to improve with the standard approach involving inhibition of cM1 and improve instead with stimulation facilitating iPMd If, however, patients who fail to improve with inhibition of cM1 also fail to improve with stimulation of iPMd, but show improvement with stimulation of cPMd, then the bimodal hypothesis – that contralesional (not ipsilesional) motor cortices are more important for severely affected patients– would be validated.

2. Methods

2.1. Subjects

We enrolled 15 patients ≥21 years of age who had experienced first-ever unilateral ischemic stroke ≥6 months prior to enrollment. Patients with hemorrhagic stroke were included if their lesion affected subcortical territories similar to those affected typically in ischemic stroke [for example, posterior limb of the internal capsule (PLIC)] (Hedna et al., 2013). We anticipated that if location of lesion following a hemorrhage were not different from location of lesion that typically follows an infarct, then the confounding effect of lesion type would be mitigated.

All patients showed weakness of the upper limb and ≥20% slowness in reaching with the paretic vs. the nonparetic limb (Harris-Love et al., 2011). We excluded patients with severe cognitive dysfunction (≤24 on the Mini-Mental State Examination, MMSE) (Folstein et al., 1983) or other neurologic/psychiatric illnesses or contraindication to TMS or magnetic resonance imaging (MRI) (Rossi et al., 2009). Patients were also excluded on account of participation in recent (≥3 months) or ongoing physical/occupational therapy or an inability to perform reaching with the paretic limb. All study procedures were in accordance with the declaration of Helsinki. All patients provided written informed consent.