Duke University School of Medicine

Doctor of Physical Therapy

Effects of Non-Invasive Brain Stimulation on Pain in Individuals with Central Post-Stroke Pain: A Systematic Review

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Background

- What is **Central Post-Stroke Pain (CPSP)**?
  - a neuropathic pain disorder resulting from an ischemic or hemorrhagic stroke that causes allodynia (pain to normally non-painful stimuli) and dysesthesia (abnormal sensation)
- Brain stimulation is a nonpharmacological treatment for patients with CPSP
- Types of relevant **non-invasive brain stimulation** (Figure 1)
  - repetitive transcranial magnetic stimulation (rTMS)
  - transcranial direct current stimulation (tDCS)

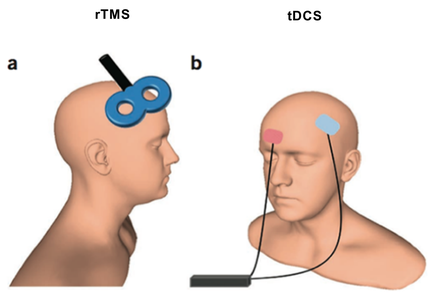

Figure 1: Examples of types of stimulation.

https://www.ninds.nih.gov/News-Events/Directors-Message/Directors-Messages/Noninvasive-Brain-Stimulation-Applications-and-Implications

Purpose

- To analyze the efficacy and quality of non-invasive brain stimulation intervention studies for CPSP in the chronic stroke population (> 6 months post stroke).

Methods

- Databases searched: PubMed, Embase, and Web of Science
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was applied
- Quality was assessed using the Modified Downs and Black checklist
- Inclusion Criteria
  - Patients (18-85 years) post stroke with CPSP
  - Randomized controlled trials and observational studies (cohort, case-control, and cross-sectional studies) published in English journals between 2007-2017
  - Non-invasive brain stimulation (tDCS or rTMS)

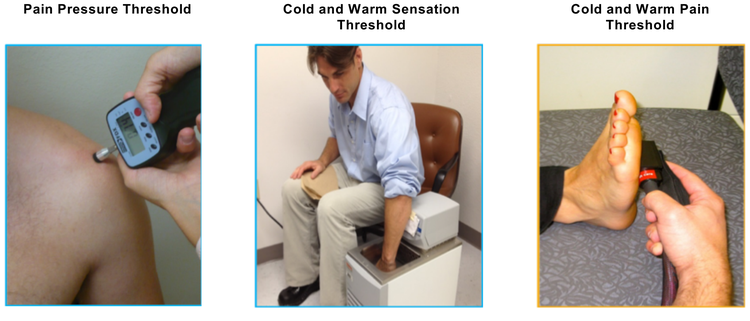

Figure 2: Examples of Quantitative Sensory Testing (QST).

http://www.24pressrelease.com/52437/news/central-nervous-system-biomarkers-industry-2018-market-research-report

Intervention Specifications and Outcomes

Author, year	Type of Stimulation	Stimulation Location	Intensity	Current flow	Frequency	Length	Control Group
Bae, S et al. 2014	tDCS	Primary motor cortex	2 mA	20 minutes	3x/week	3 weeks	Sham tDCS
De Oliveira, R et al. 2014	rTMS	Primary Motor Cortex/ Dorsolateral Prefrontal Cortex	120% RMT	10 Hz - 25 x 5 sec	1x/day	10 days	Sham rTMS
Hasan, M et al. 2014	rTMS	M1 predetermined 'hotspot'	80-90% RMT	10 Hz - 20 x 10 sec	1 session/ 3-5 days	5 sessions	None
Kobayashi, M et al. 2015	rTMS	Primary motor cortex	90% RMT	5 Hz - 10 x 10 sec	1x/week	12 weeks	Sham rTMS
Matsumura, Y et al. 2013	rTMS	Primary motor cortex	100% RMT of unaffected side	5 Hz - 10 x 50 pulses	1 session	1 day	Sham rTMS
Ohn, S et al. 2012	rTMS	Motor 'hotspot' of first dorsal interossei of affected hand	90 % RMT	10 Hz - 50 x 5 sec	1/day	5 days	None

Table 1. Data of interventions from included studies. RMT = Resting Motor Threshold

Author, year	Measurement Time Points	VAS Differences (P<.05)	QST Differences (P<.05)
Bae, S et al. 2014	Baseline, immediate post	No	No
	Baseline, 1 week post	No	**Yes**
	Baseline, 3 weeks post	**Yes**	**Yes**
De Oliveira, R et al. 2014	Baseline, Day 10 post	No	Not recorded in study
Hasan, M et al. 2014	Baseline, immediate post	**Yes**	**Yes**
Kobayashi, M et al. 2015	Baseline, immediate post	**Yes**	Not recorded in study
	Baseline, weekly for 12 weeks	**Yes**	Not recorded in study
Matsumura, Y et al. 2013	Baseline, multiple time points post (0, 60, 120, 180, 240, 300 min, and 24 hours)	**Yes** (significant time course effect up to 300 min)	Not recorded in study
Ohn, S et al. 2012	Baseline, immediately post	**Yes**	Not recorded in study

Table 2. Interventions results from included studies. VAS = Visual Analog Scale; QST = Quantitative Sensory Test

Results

Search Results
- 1107 articles found in initial search; 6 articles eligible for inclusion

Study Parameters (Table 1)
- Five studies utilized rTMS; one used tDCS
- Five studies stimulated over primary motor cortex, while one stimulated over pre-motor cortex and dorsolateral prefrontal cortex

Outcome Measures
- Clinical pain: five studies utilized VAS
- Experimental pain: two studied utilized QST (Figure 2)

Brain Stimulation Effects (Table 2)
- Five studies found a decrease in clinical pain intensity (p<.05) from immediately after, to 3 weeks after, rTMS or tDCS delivered over the primary motor cortex
- One study tested rTMS to the left premotor/dorsolateral prefrontal cortex and failed to find a treatment effect for clinical pain (p>.05)
- For experimental pain, one study found thermal pain thresholds improved for those receiving tDCS compared to sham (p<.05); while another study found normalization of the cold detection threshold only after rTMS (p<.05)

Quality Assessment (Table 3)
- Only one study found to be of 'excellent/good' quality, while the other five were rated as either 'fair' or 'poor'

	Bae, S et al. 2014	De Oliveira, R et al. 2014	Hasan, M et al. 2014	Kobayashi, M et al. 2014 - Study 1	Kobayashi, M et al. 2014 - Study 2	Matsumura, Y et al. 2013	Ohn, S et al. 2012
Reporting	7	10	6	8	8	7	8
External Validity	0	0	0	0	0	0	0
Internal Validity Bias	5	7	4	5	5	3	4
Internal Validity Confounding	1	4	0	3	3	0	2
Power	0	1	0	0	0	0	1
Total	**13**	**22**	**10**	**16**	**16**	**10**	**15**

Table 3. Quality assessment, Modified Downs and Black Checklist

Key: Poor (<14) | Fair (14-18) | Excellent/Good (19-28)

Conclusions

- Non-invasive brain stimulation may have a therapeutic effect on pain levels, as evidenced by decreased VAS and QST scores
- Poor quality of the studies reviewed, and significant variation in parameters of stimulation and participant characteristics raises caution for drawing conclusions
- Future studies in this area should focus on standardizing treatment parameters, improving the homogeneity of the populations studied, and understanding if non-invasive brain stimulation is a sustainable long-term treatment for patients with CPSP

Clinical Relevance

- rTMS and tDCS may be effective non-invasive treatment options to reduce pain in persons with CPSP, and may provide a window of time for decreased pain and optimization of therapy treatments
- Clinicians should consider quality of evidence and length of effects

References available upon request