Noninvasive brain stimulation in neurorehabilitation

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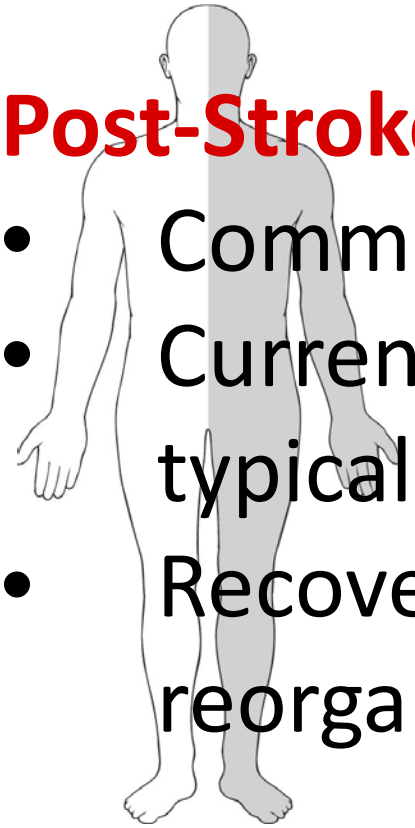
NIBS in post-stroke neurorehabilitation

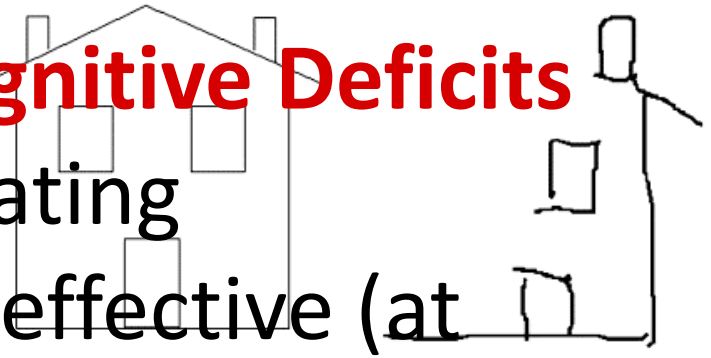


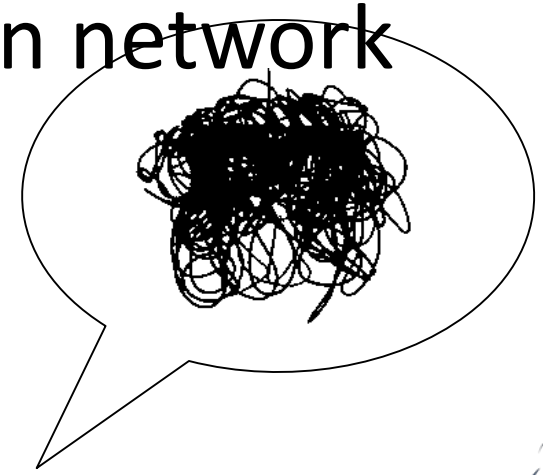
Paresis

Post-Stroke Motor & Cognitive Deficits

- Common and debilitating
- Current therapies: Ineffective (at typical doses)
- Recovery depends on network reorganization

Visuospatial Neglect





Aphasia

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How do intact cognitive systems systems work?

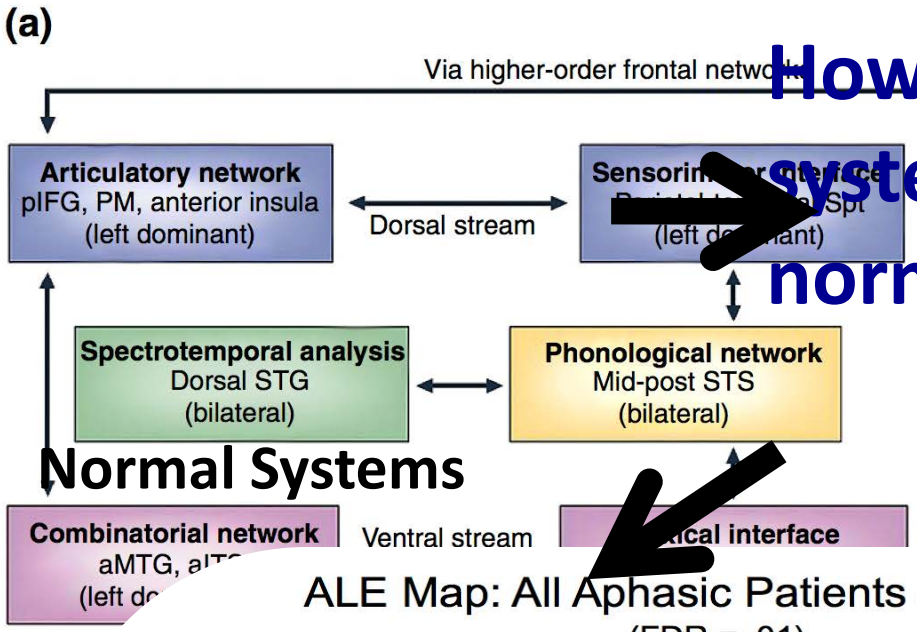
How do injured systems differ from normal systems?

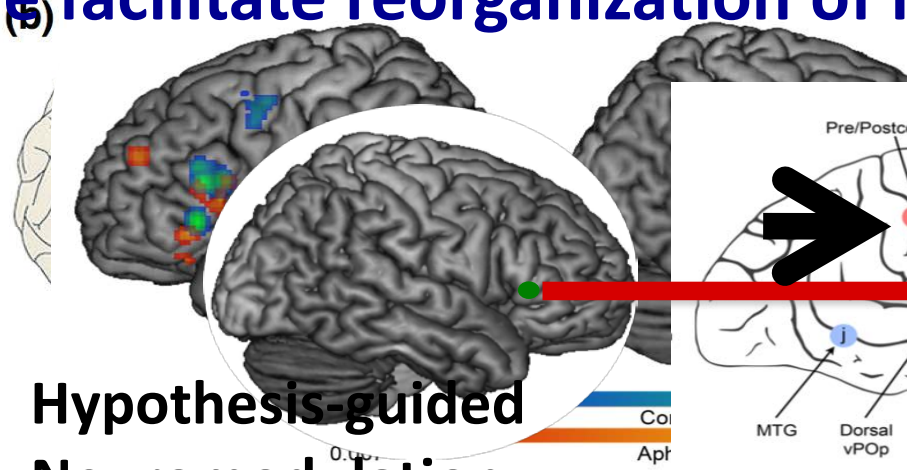
Can we facilitate reorganization of injured neural systems?

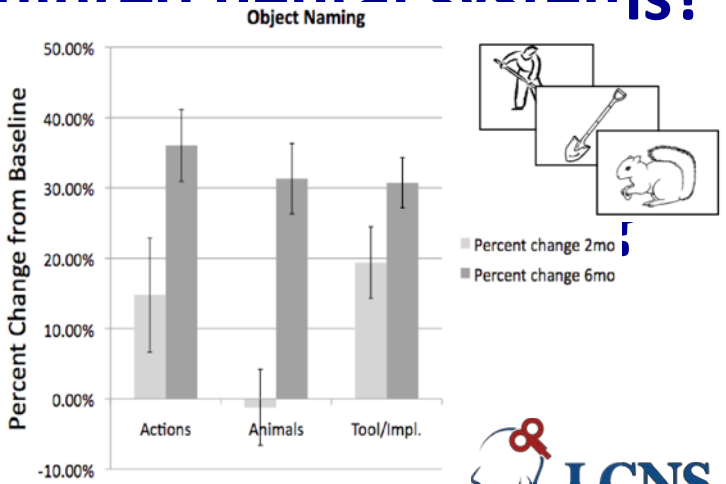
Reorganized Systems

Normal Systems

Cognitive Outcomes







Hypothesis-guided Neuromodulation

Turkeltaub et al. *Neurology*, 2011

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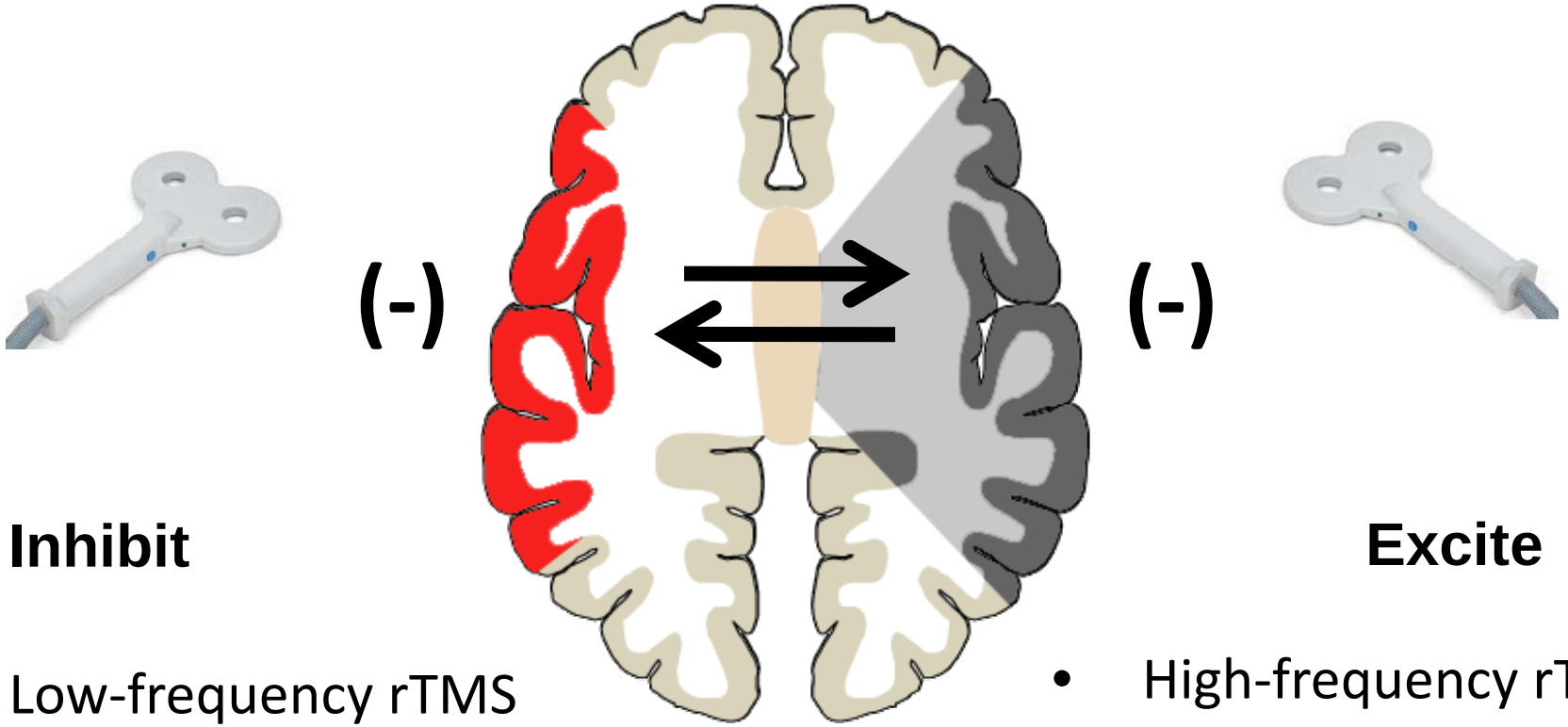
Interhemispheric Inhibition Model



Inhibit

- Low-frequency rTMS
- Cathodal tDCS

Excite

- High-frequency rTMS
- Anodal tDCS

Adapted from Hamilton et al., 2011

"All models are wrong, but some are useful"
-George E.P. Box

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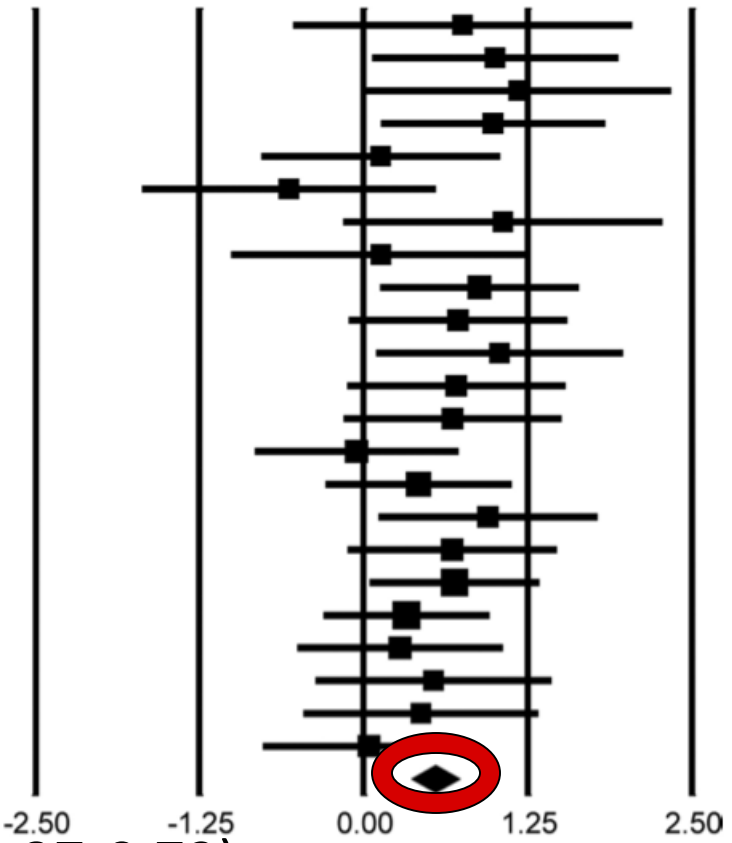
TMS Studies in Post-stroke Paresis

Study name	Effect size	Lower limit	Upper limit	p-Value	Relative weight
Mansur et al, 2005	0.75	-0.53	2.03	0.25	1.88
Takeuchi et al, 2005	1.00	0.07	1.93	0.04	3.58
Fregni et al, 2006	1.18	0.02	2.33	0.05	2.33
Leipert et al, 2007	0.98	0.14	1.83	0.02	4.31
Malcolm et al, 2007	0.13	-0.77	1.03	0.78	3.81
Pomeroy et al, 2007	-0.57	-1.68	0.54	0.32	2.50
Talelli et al, 2007 (iTBS)	1.06	-0.15	2.27	0.09	2.12
Talelli et al, 2007 (cTBS)	0.13	-1.00	1.26	0.82	2.41
Nowak et al, 2008	0.88	0.13	1.63	0.02	5.51
Dafotakis et al, 2008	0.72	-0.11	1.54	0.09	4.54
Takeuchi et al, 2008	1.03	0.10	1.97	0.03	3.55
Khedr et al, 2009 (1 Hz)	0.70	-0.12	1.53	0.10	4.55
Khedr et al, 2009 (3 Hz)	0.68	-0.15	1.50	0.11	4.57
Ameli et al, 2009 (cortical)	-0.06	-0.82	0.71	0.89	5.23
Ameli et al, 2009 (subcortical)	0.42	-0.28	1.12	0.24	6.31
Khedr et al, 2010 (3 Hz)	0.95	0.12	1.77	0.03	4.52
Khedr et al, 2010 (10 Hz)	0.67	-0.12	1.46	0.10	4.95
Emara et al, 2010 (1Hz)	0.69	0.05	1.33	0.03	7.60
Emara et al, 2010 (5 Hz)	0.32	-0.30	0.95	0.31	7.95
Chang et al, 2010	0.28	-0.50	1.05	0.49	5.13
Ackerley et al. 2010 (iTBS)	0.53	-0.36	1.42	0.24	3.89
Ackerley et al. 2010 (cTBS)	0.43	-0.45	1.32	0.34	3.93
Theilig et al, 2011	0.04	-0.76	0.84	0.92	4.83
(Fixed effects model)	0.55	0.37	0.72	0.00	



Effect size (All studies): 0.55; 95% CI (0.37-0.72)

Effect size (Contralesional rTMS): 0.69; 95% CI (0.42-0.95)

Hsu et al., *Stroke*, 2012

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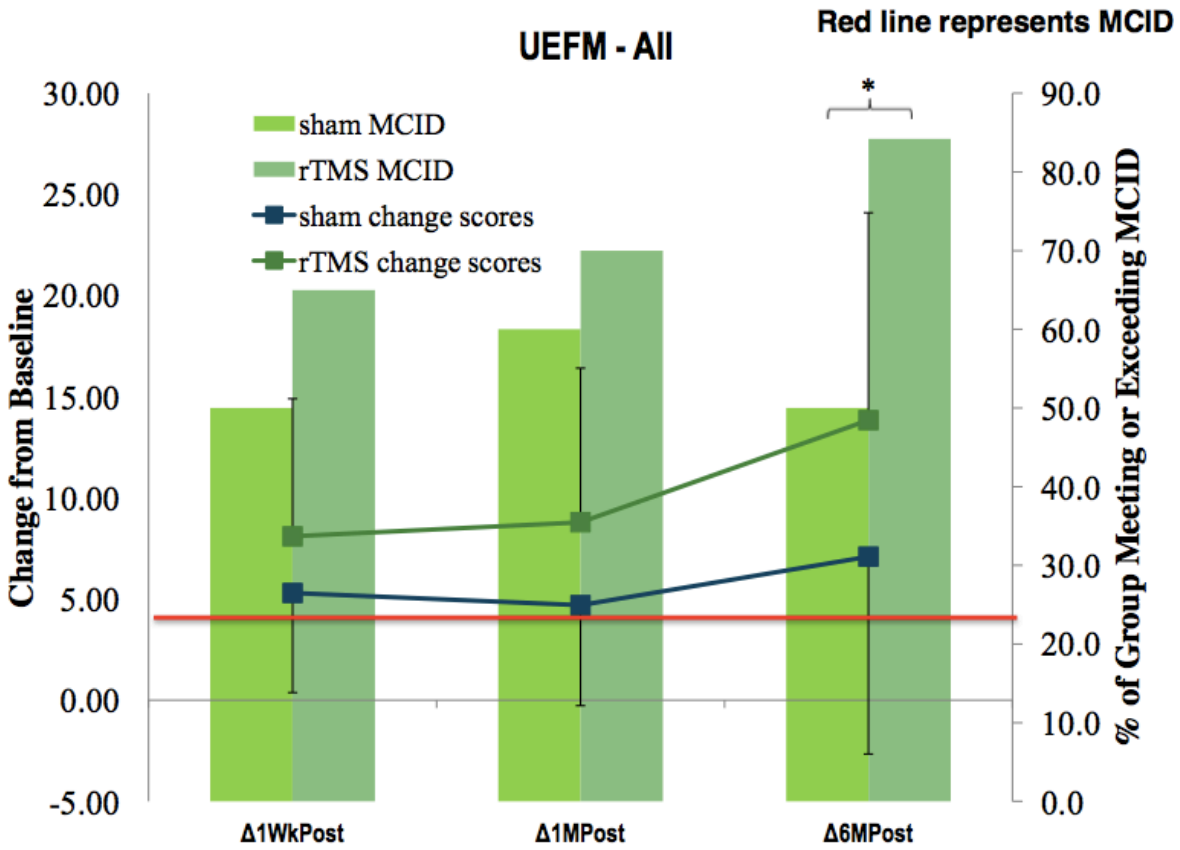
Contrastim and NICHE



Harvey et al., 2014, *AHA/ASA International Stroke Conference*

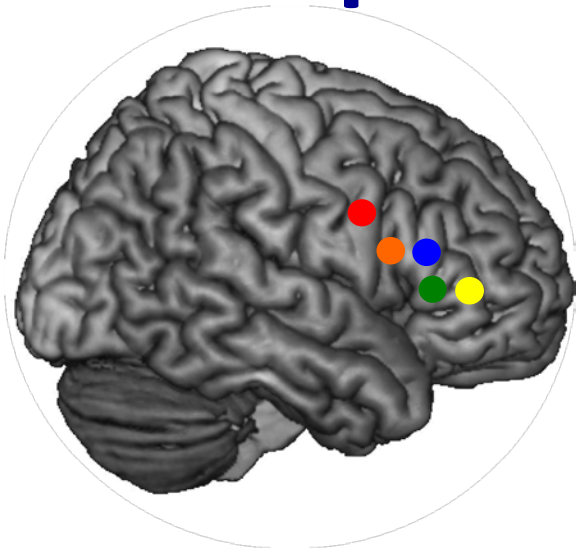
- Contralesional rTMS + OT vs sham +OT
- 20 rTMS/10 Sham
- 18 sessions/6 weeks
- 1 week, 1 month, 6 month follow-up

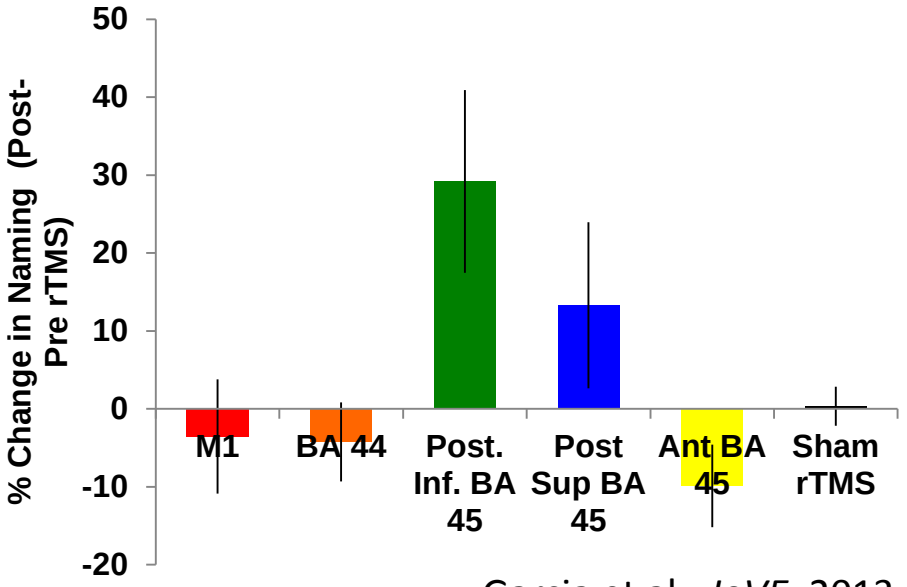
- 80% Clinically meaningful response rate

- Navigated Inhibitory rTMS in Contralesional Hemisphere Evaluation (NICHE)
  - Phase III trial
  - 2 years
  - 12 sites

RIC
Rehabilitation Institute of Chicago

rTMS in Aphasia

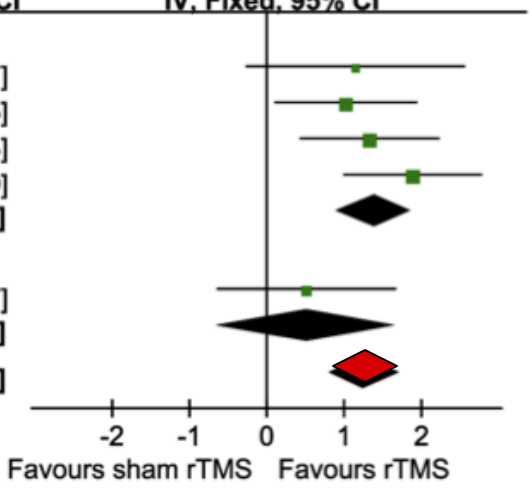




Garcia et al., *JoVE*, 2013

Study or Subgroup	Real rTMS Mean	SD	Total	Sham rTMS Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
The global ATT score								
Weiduschat N 2011	19.83	8.2	6	8.5	9.95	4	10.1%	1.15 [-0.27, 2.57]
Hartmann A 2013	22.8	12.36	11	9.4	12.79	10	24.0%	1.02 [0.10, 1.95]
Thiel A 2013	23.6	12.15	13	7.55	11	11	25.1%	1.33 [0.43, 2.23]
Heiss WD 2013	22.4	1.77	15	8.6	10.06	14	25.4%	1.89 [0.99, 2.79]
Subtotal (95% CI)			**45**			**39**	**84.8%**	**1.39 [0.90, 1.88]**
The global BDAE score								
Barwood CHS 2013	18.5	36.68	6	0.17	28.73	6	15.2%	0.51 [-0.65, 1.67]
Subtotal (95% CI)			**6**			**6**	**15.2%**	**0.51 [-0.65, 1.67]**
Total (95% CI)			**51**			**45**	**100.0%**	**1.26 [0.80, 1.71]**

Heterogeneity: Chi² = 3.79, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 5.44 (P < 0.00001)
Test for subgroup differences: Chi² = 1.86, df = 1 (P = 0.17), I² = 46.3%



Ren et al., *PLOS One*, 2014

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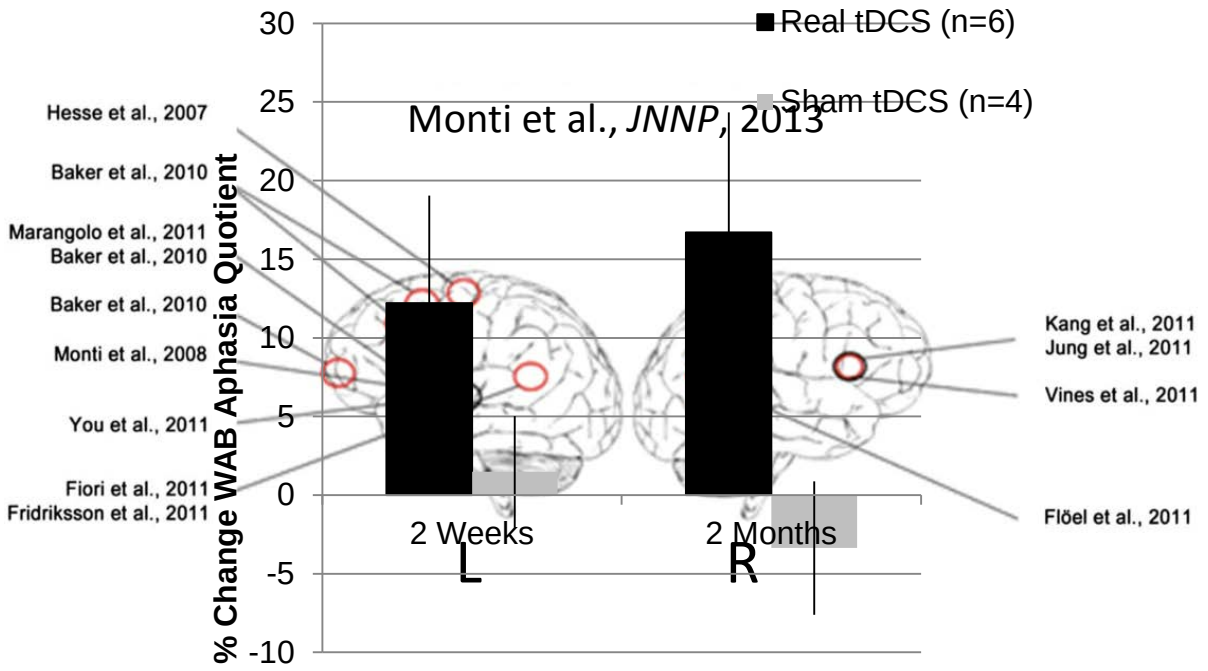
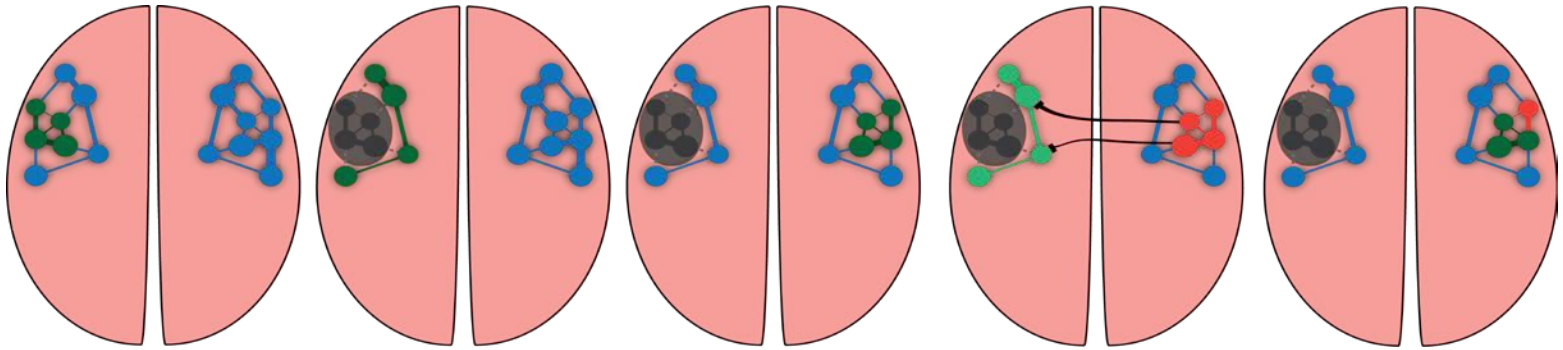
tDCS in Aphasia: Promising But Preliminary

- Small samples
- Clinical Heterogeneity
  - -Aphasia type
  - -Chronicity
- Variable Parameters
- Limited Follow-up
- Promising studies ongoing (e.g. Fridriksson)





Multiple Mechanisms of Aphasia Recovery

Adapted from Torres et al., 2013

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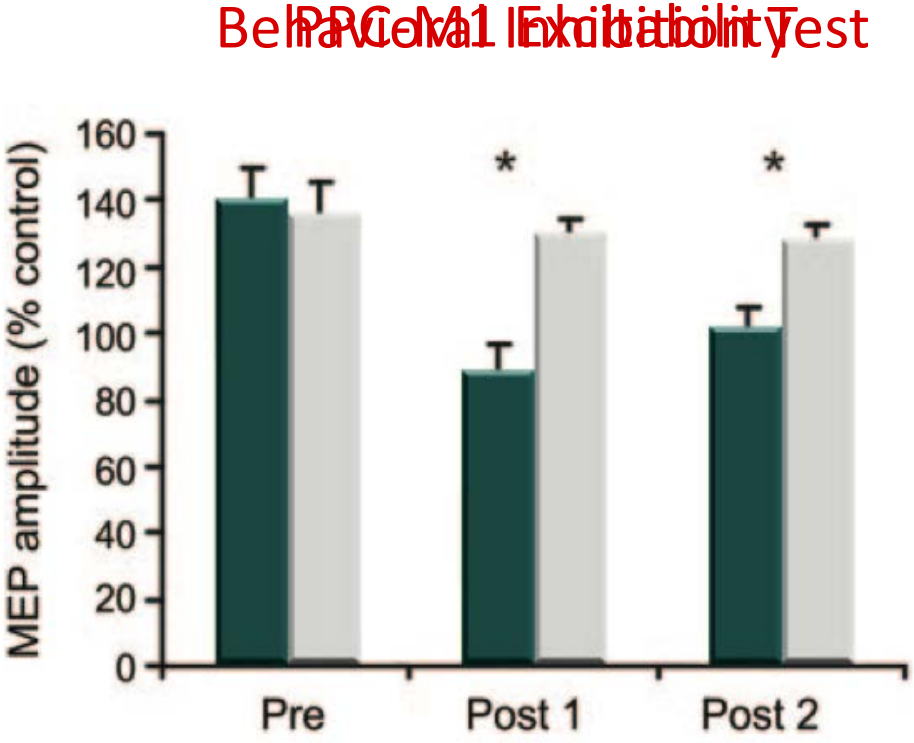
Koch et al., 2012

Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect

- Randomized, double-blind, sham-controlled
- 10 sessions cTBS over 2 weeks
- Intact left parietal cortex
- 2 week & 4 week follow-up (post-initiation of therapy)
- 18 subacute ischemic stroke
- Behavioral Inattention Test
- Bifocal TMS to assess fronto-parietal excitability



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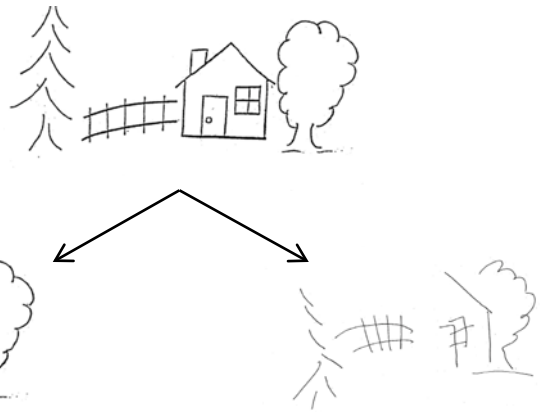
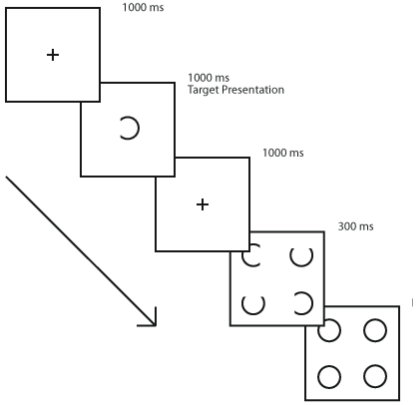
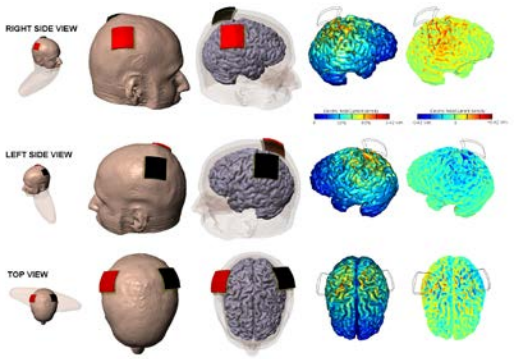
tDCS Enhances Spatial Processing

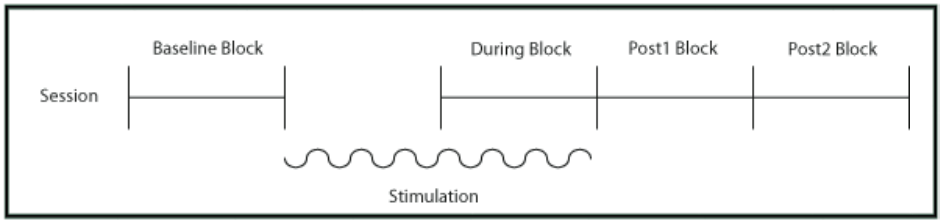


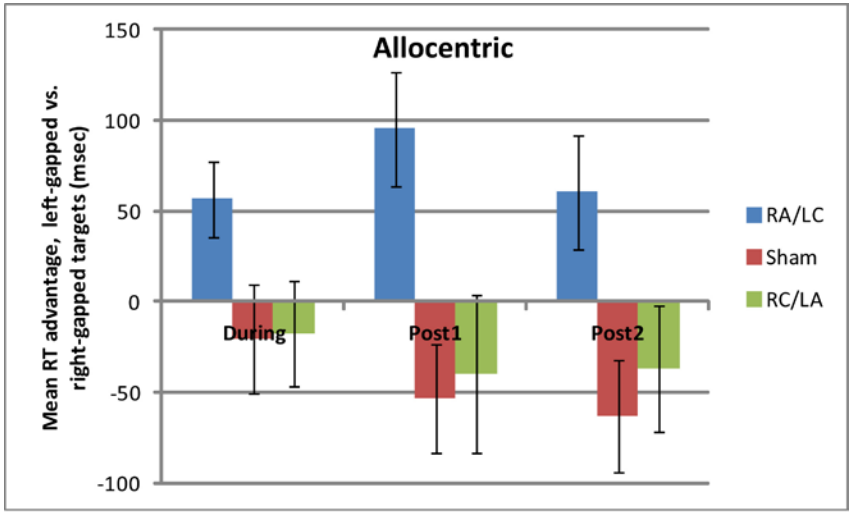
Egocentric Neglect

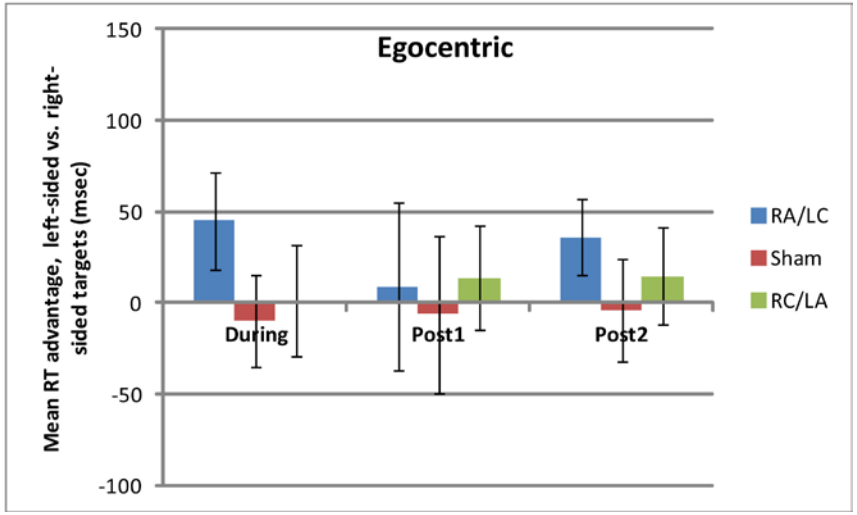
Allocentric Neglect











Medina et al., 2012

Challenges to NIBS in Rehab

- No FDA-approved rehab indications to date
- Much research at proof-of-concept stage

Challenges to clinical development of TMS/tDCS

- **Phase I:**
  - Dose-effect relationships
  - Testing of potentially risky populations
- **Phase II/III:**
  - Recruitment/eligibility challenges
  - Heterogeneous patient populations
  - Multiple sessions & attrition
- **Phase III:**
  - Control group and blinding issues
  - Heterogeneity of approaches
  - Small sample sizes/single sites

FDA Clinical Trial Phases:

Phase I: Screening for safety

Phase II: Smaller, controlled trials of efficacy

Phase III: Pivotal larger studies of safety and efficacy*

*Two positive phase III trials are required for FDA approval.

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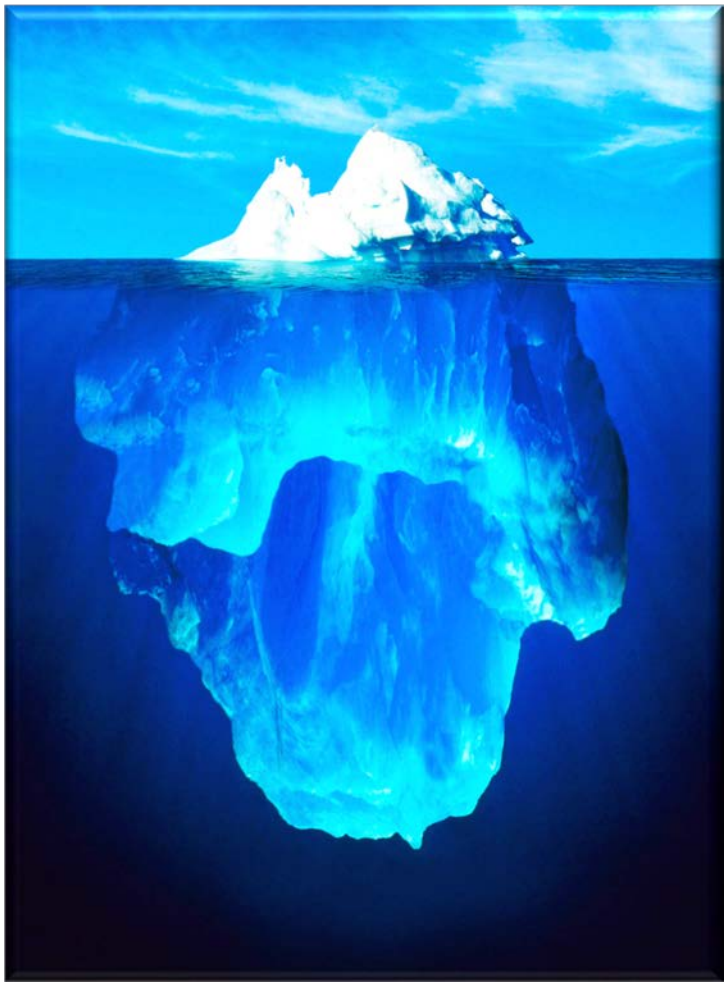
Other applications in brain injury

- TMS as a prognostic indicator of stroke outcomes
  - Motor tract patency
  - Marker of plasticity
- TMS pre-surgical mapping of motor function and language
- NIBs to treat motor, cognitive, neuropsychological disorders associated with TBI



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