Stimulating Conversations: Noninvasive Neuromodulation of Language Networks to Characterize and Treat Aphasia

No relevant financial conflicts

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Funding agencies
Topics

• Mechanisms of recovery in post-stroke aphasia
• TMS for post stroke aphasia
• tDCS for post-stroke aphasia
• tDCS for neurodegenerative aphasias
How do intact cognitive systems work?

How do injured systems differ from normal systems?

Can we facilitate reorganization of injured neural systems?

Hypothesis-guided Neuromodulation

Turkeltaub et al. Neurology, 2011
He had lost his speech; he could only say "Haw-haw." He could cry vigorously; there was no lack of voice. From his admission, he appeared to understand all that was said to him. When asked when he began to speak, he looked about for the questioner's tongue; counted four, when asked how many children he had; and six, when asked his age. He occasionally smiled reflectively. There was at first no approach to a voluntary articulate sound, but the words "ah" and "ah-ah" were attempted, and were correct.

From the first, he was able to write his name when asked; and after a few months would answer in writing any question that was put to him. He could not be induced to show his teeth, nor to protrude his lips, or to smile when he was told. But his face was not expressionless. He occasionally smiled reflectively. There was at first no approach to a voluntary articulate sound, but the words "ah" and "ah-ah" were attempted, and were correct.

On the evening of the 17th of November, we found him more improved; he could make sounds, and a phonetic sound was heard on the throat. He could cry slightly, but not loudly. The voice was not as distinct as on the previous day. He could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 18th, he was less improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 19th, he was more improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 20th, he was greatly improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 21st, he was less improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 22nd, he was more improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 23rd, he was greatly improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 24th, he was less improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 25th, he was more improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 26th, he was greatly improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 27th, he was less improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 28th, he was more improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 29th, he was greatly improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head. On the evening of the 30th, he was less improved; he could make a slight movement of the head, but not of the body. He could not move his limbs, but could move his arms and legs, and could make a slight movement of the head.
Postman-Caucheteux et al., 2010

T-stat = 5

a. Incorrect responses
b. Correct responses
c. Incorrect-correct
d. Correct-incorrect

p < .0
Homologues, homotopes, and noncontributors...
Transcranial Magnetic Stimulation (TMS)

- High resolution
- Excites or inhibits
- Pulses and patterns
- Low risk of seizure
- LTP-like long-term effects
Baseline testing & MRI → Sitefinding

1 Hz = Inhibitory Stimulation
Narrative length (seconds)

Number of Items

Unique Nouns
Total Nouns
Total Verbs
Unique Words
Unique Verbs

Pre TMS
Post TMS

Medina et al., Brain Stimulation, 2013
Shah-Basak, Wurzman, et al., 2016
Garcia et al., JoVE, 2013
A noisy node?

Phase 2 clinical trial (PI: Coslett) now enrolling
Is the RH’s role monolithic?

NO!
Help?
Hurt?
Both?
Nothing?
What principles determine where to go?
Cognitive localization in the brain is a function of local and global connectivity.

**Network control theory** allows inferences about the operational utility of brain centers.

**Hypothesis 1:** Language control relies on the network controllability properties of language centers.

**Hypothesis 2:** After injury of the LH language centers, recruitment of new sites may depend on their network control properties.

*Gu et al., 2015*
Different cognitive tasks $\rightarrow$ different control demands

Closed Ended: Modal Control?

Open Ended: Boundary Control?

Medaglia et al., *J. Neuroscience*. 2018
50 Hz @ 5Hz

Medaglia et al., J. Neuroscience. 2018
**Boundary Control**

Open tasks

- Low Boundary
- High Boundary

**Modal Control**

Closed tasks

- Low Modal
- High Modal

Medaglia et al., *J. Neuroscience*. 2018
Using network controllability to guide treatment
Transcranial Direct Current Stimulation (tDCS)

- Subthreshold
- Alters firing rates
- Anodal vs. cathodal
- Inexpensive & safe
- Combines with therapies
- LTP-like long-term effects
Membrane polarization effects

CM = Cell Membrane

de Berker et al., 2013
The right tool for a messy job?

Turkeltaub et al., Neurology, 2011
tDCS effects facilitates reading

**Reading Efficiency**

- 25 normal right-handed
- Anode over left pTC; cathode over right pTC
- 2 sessions: (1) real tDCS (1.5mA for 20 min), and (2) sham tDCS.
- Standardized word and nonword reading tests

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Turkeltaub et al. *Brain Stimulation*, 2011
Left angular gyrus mediates conceptual combination in language

Price et al., JoN 2016
Monti et al., JNNP, 2013


N=122 patients

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study design</th>
<th>Stroke chronicity</th>
<th>Treated - tDCS</th>
<th>Control - Sham</th>
<th>Sample Size</th>
<th>Std diff in means Random 95% CI</th>
<th>Std error</th>
<th>p-value</th>
<th>Forest Plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polanowska et al. (2013)</td>
<td>Between</td>
<td>Subacute</td>
<td>Mean(SD) 39.8(25.1) Mean(SD) 50.1(24.5)</td>
<td>Mean(SD) 38.7(22.9) Mean(SD) 43.9(23.6)</td>
<td>14</td>
<td>Mean(SD) 24.59(10.01)</td>
<td>0.257</td>
<td>[0.56, 1.07]</td>
<td>0.42</td>
</tr>
<tr>
<td>You et al. (2011) a-tDCS</td>
<td>Between</td>
<td>Subacute</td>
<td>Mean(SD) 2.43(3.55) Mean(SD) 9.57(9.62)</td>
<td>Mean(SD) 7.00(2.65) Mean(SD) 6.43(10.01)</td>
<td>7</td>
<td>Mean(SD) 2.02(0.85, 1.25)</td>
<td>0.202</td>
<td>[0.85, 1.25]</td>
<td>0.54</td>
</tr>
<tr>
<td>You et al. (2011) c-tDCS</td>
<td>Between</td>
<td>Subacute</td>
<td>Mean(SD) 2.43(4.16) Mean(SD) 13.57(17.51)</td>
<td>Mean(SD) 1.00(2.65) Mean(SD) 6.43(10.01)</td>
<td>7</td>
<td>Mean(SD) 0.41(0.65, 1.47)</td>
<td>0.411</td>
<td>[0.65, 1.47]</td>
<td>0.54</td>
</tr>
<tr>
<td>Jung et al. (2011)</td>
<td>Within</td>
<td>Mixed</td>
<td>Mean(SD) 24.84(22.60) Mean(SD) 39.65(28.11)</td>
<td>Mean(SD) 24.84(22.60) Mean(SD) 39.65(28.11)</td>
<td>37</td>
<td>Mean(SD) 0.552(0.35, 0.75)</td>
<td>0.11</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Santos et al. (2013)</td>
<td>Within</td>
<td>Chronic</td>
<td>Mean(SD) 4.18(5.33) Mean(SD) 5.18(5.00)</td>
<td>Mean(SD) 4.18(5.33) Mean(SD) 5.18(5.00)</td>
<td>19</td>
<td>Mean(SD) 0.193(0.26, 0.65)</td>
<td>0.23</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Bakor et al. (2010)</td>
<td>Crossover</td>
<td>Chronic</td>
<td>Mean(SD) 27.3(17.16) Mean(SD) 31.3(19.39)</td>
<td>Mean(SD) 28.6(18.18) Mean(SD) 28.9(18.63)</td>
<td>10</td>
<td>Mean(SD) 1.064(0.31, 2.44)</td>
<td>0.70</td>
<td>0.13</td>
<td></td>
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<tr>
<td>Kang et al. (2011)</td>
<td>Crossover</td>
<td>Chronic</td>
<td>Mean(SD) 28.4(6.9) Mean(SD) 31.9(6.9)</td>
<td>Mean(SD) 26.36(6.1) Mean(SD) 29.9(6.2)</td>
<td>10</td>
<td>Mean(SD) 0.503(0.02, 0.98)</td>
<td>0.25</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Volpato et al. (2013)</td>
<td>Crossover</td>
<td>Chronic</td>
<td>Mean(SD) 87.97(13.26) Mean(SD) 85.63(16.35)</td>
<td>Mean(SD) 86.88(17.72) Mean(SD) 86.88(17.72)</td>
<td>8</td>
<td>Mean(SD) 0.170(0.11, 0.45)</td>
<td>0.14</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Flöel et al. (2011) a-tDCS</td>
<td>Crossover</td>
<td>Chronic</td>
<td>Mean(SD) 93.45(4.99) Mean(SD) 88.91(8.67)</td>
<td>Mean(SD) 93.45(4.99) Mean(SD) 88.91(8.67)</td>
<td>11</td>
<td>Mean(SD) 0.502(0.13, 0.87)</td>
<td>0.19</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Flöel et al. (2011) c-tDCS</td>
<td>Crossover</td>
<td>Chronic</td>
<td>Mean(SD) 91.82(9.24) Mean(SD) 88.91(8.67)</td>
<td>Mean(SD) 91.82(9.24) Mean(SD) 88.91(8.67)</td>
<td>11</td>
<td>Mean(SD) 0.322(0.08, 0.56)</td>
<td>0.13</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Overall

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Std diff in means Random 95% CI</th>
<th>Std error</th>
<th>p-value</th>
<th>Forest Plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>0.395 [0.28, 0.51]</td>
<td>0.06</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Q=7.43, df=9 (p=0.592), I²=2=0%

Test for overall effect: Z=6.55, p<0.0001


342 records identified:
PubMed n=43, CENTRAL n=22, Embase n=31, ScienceDirect n=188, lex=med@Ovid n=58, 0 additional records identified from clinicaltrials.gov

281 non-duplicate records

246 records excluded:
• Not tDCS treatment studies (n=140)
• Reviews, book chapters, case studies (n=61)
• Non-stroke patients (n=50)
• <3 tDCS sessions on the same site (n=7)
• Missing full-text or non-English (n=3)

17 records assessed for eligibility

9 full text articles excluded:
• Multiple publications of the same trial (n=3)
• Picture naming accuracy not reported (n=8)
• Unable to extract data (n=1)

8 studies included in final analysis
Larger, more rigorous studies

Randomized, sham-controlled study of naming in post-stroke aphasia

Fridriksson et al., 2018
Novel targets

Marangolo et al., 2017
tDCS to treat PPA

Wilson, S. M. et al., 2012

Baseline language test

Post language test

Non-fluent variant PPA
Semantic variant PPA
Logopenic variant PPA
- N=4 lvPPA; 2 naPPA
- Left frontal anode; parietal cathode
- 10 days; 1.5 mA x 20 minutes; 25 cm² pads

Hosseini et al., 2018

N=6 (3 lvPPA; 3 naPPA)

Hosseini et al., 2018
Global Performance

McConathey et al., 2017
tDCS + Semantic Feature Training

- $N=3$ svPPA; $N=1$ lvPPA; $N=1$ AD (anomia)
- 2 Weeks (10 days) of treatment
- Left parietal anode; forehead cathode
- 1.5 mA x 20 minutes; 25 cm$^2$ pads

_Hung et al., 2017_
Conclusions

• A bihemispheric post-stroke language network.
• Focal manipulation of a “noisy node” with TMS enhances language performance.
• Network control properties may inform which are the best nodes to manipulate.
• Diffuse DC stimulation may facilitate recovery in post-stoke aphasia and PPA.
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Long term potentiation

- Effects persisted 1 week later
- Directly related to epigenetic regulation of BDNF expression
- tDCS enhances **activity-dependent** changes in synaptic connectivity

Podda et al., 2015
WAB Aphasia Quotient Scoring

- 0-25 = very severe
- 26-50 = severe
- 51-75 = moderate
- 76 and above = mild

Baseline abilities influence tDCS effects

Norise et al., 2017