tDCS in Clinical Disorders

HBM Educational course „Brain Stimulation: Past, Present and Future“
Hamburg, June 8th, 2014

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Outline

Introduction
- Decline in cognitive functions, particularly learning ability, over the lifespan
- Increase in aging-associated diseases like dementia and stroke
- Overview training-adjuvant therapies
- Why use transcranial direct current stimulation in the clinical context?

atDCS in neuropsychiatric disease
- Healthy volunteers, proof-of-principle
- MCI/Alzheimer’s Disease
- Aphasia

Open questions and outlook
Further reading

Review

tDCS-enhanced motor and cognitive function in neurological diseases

Agnes Flöel *

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Review

Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases

Min-Fang Kuo, Walter Paulus, Michael A. Nitsche *

University Medical Center, Clinic for Clinical Neurophysiology, Georg-August-University, Robert-Koch-Str. 40, 37079 Goettingen, Germany
Cognitive functions over the lifespan

Seattle Longitudinal Study

Hedden and Gabrieli, Nat Rev Neurosci 2004
Increase in stroke and dementia in aging societies

Pendlebury et al, Maturitas 2010
Alzheimer’s dementia and its precursor, mild cognitive impairment

Clinical criteria, MCI
- Memory complaint
- Memory impaired for age
- Normal general cognitive function
- Normal activities of daily living

Clinical criteria, AD
- Memory complaint
- Memory and at least one other cognitive domain impaired
- Impaired activities of daily living

→ core symptoms: deficits in learning and memory formation

Enhanced learning success by means of adjuvant interventions?
Post-stroke aphasia

20% of surviving stroke patients
$\rightarrow$ permanent deficits in language function

Training in chronic stage of aphasia?
$\rightarrow$ at least 9 hours/week needed for improvement

Enhanced training success by means of adjuvant interventions?

*Pedersen et al, Ann Neurol 2004*

*Bhogal et al, 2003 Stroke*
Adjuvant interventions to increase learning ability „neuroplasticity“ in neurological and psychiatric disorders

- Non-invasive brain stimulation
  - repetitive transcranial magnetic stimulation (rTMS)
  - transcranial direct current stimulation (tDCS)
  - ...

- Pharmacological neuromodulation
  - amphetamine
  - levodopa
  - donepezil
  - memantine
  - G-CSF, EPO
  - ...

- Endogenous learning modulation
  - physical activity
  - dietary factors
  - ...

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Non-invasive brain stimulation

Transcranial direct current stimulation, tDCS

tDCS
Modulation of resting membrane potential

- Release of nerve growth factors and neurotransmitters (Fritsch et al, Neuron 2010)
- Increase in cerebral blood flow and metabolism (Kay and Wright, J Neurophysiol 2013; Floel et al, Neuroimage 2014)
tDCS in patient studies

*Easy Applicability, Safety & Comfort*

- Electrode size
  - 5 x 7cm (active),
  - 10cm x 10cm (reference)

- Constant current
  - 1 mA, 20 min

- Tingling on the scalp, fades after around 10-20 sec
  - high comfort, applicable in parallel to training sessions

- No seizures induced so far

- Small device, may be carried around by patient during training sessions (e.g., motor training)

- Possible to blind participants and person applying stimulation *(Stagg and Nitsche, Neuroscientist 2011)*
## tDCS in patient studies

**Easy Applicability, Safety & Comfort**

<table>
<thead>
<tr>
<th></th>
<th>tDCS</th>
<th>rTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality of sensations</strong> (Anand and Hotson, 2002; Hummel et al., 2005a; Paulus, 2003)</td>
<td>No sound, mild transient tingling sensations, no twitches</td>
<td>Sound, tingling, muscle twitch under the coil if suprathreshold</td>
</tr>
<tr>
<td><strong>Duration of sensation</strong> (Anand and Hotson, 2002; Hummel et al., 2005a; Paulus, 2003)</td>
<td>Only in the initial few seconds of application, then fades</td>
<td>All along application</td>
</tr>
<tr>
<td><strong>Discomfort of sensations</strong> (Hummel et al., 2003a)</td>
<td>Transient and mild</td>
<td>Mild if subthreshold Higher if suprathreshold</td>
</tr>
<tr>
<td><strong>Focality of stimulation</strong> (Jahanbakhsh and Rothwell, 2000; Nietzsche and Paulus, 2003)</td>
<td>Less focal</td>
<td>More focal</td>
</tr>
<tr>
<td><strong>Duration of modulatory effects</strong> (Huang and Rothwell, 2004; Hummel et al., 2005; Nietzsche et al., 2002)</td>
<td>From seconds to hours</td>
<td>From seconds to hours</td>
</tr>
<tr>
<td><strong>Time resolution</strong> (Paulus, 2003; Siebner and Rothwell, 2003)</td>
<td>Poor: seconds</td>
<td>Excellent: milliseconds</td>
</tr>
<tr>
<td><strong>Capacity to elicit a virtual lesion</strong> (Jahanbakhsh and Rothwell, 2000; Siebner and Rothwell, 2003, Antal et al. 2004)</td>
<td>Less tested, but promising</td>
<td>Well documented</td>
</tr>
<tr>
<td><strong>Ease of design sham-controlled double-blind studies</strong> (Hummel, 2005a; Linabry 2001)</td>
<td>Less difficult</td>
<td>More difficult</td>
</tr>
<tr>
<td><strong>Ability to administer simultaneously with motor training</strong></td>
<td>Easily done</td>
<td>More difficult</td>
</tr>
<tr>
<td><strong>Safety of intervention</strong> (Hummel et al., 2005a; Nietzsche et al., 2003a; Wassermann, 1998)</td>
<td>Safe if far but further studies needed</td>
<td>Well documented</td>
</tr>
<tr>
<td><strong>Simplicity of application</strong></td>
<td>Easily applied</td>
<td>Easily applied, requires additional holder to keep coil in constant position</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Lower</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Gandiga et al, Clin Neurophysio 2006
Learning improvement
atDCS

Learning of a novel vocabulary, single session

1 mA tDCS 20 min

<table>
<thead>
<tr>
<th></th>
<th>correct</th>
<th>incorrect</th>
</tr>
</thead>
<tbody>
<tr>
<td>block 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>block 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>block 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>block 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anodal vs Cathodal vs Sham

see also Fiori et al, J Cogn Neurosci 2010
Does atDCS lead to sustained gains in learning?

Holland and Crinion, Aphasiology 2011
atDCS

Learning of novel motor skills, multiple sessions and sustained effects

Reis et al, PNAS 2009
for language learning: see Meinzer et al, Cortex 2014
Learning enhancement in patients with MCI or dementia?
atDCS in patients with Alzheimer’s Disease

single-session

Table 1 Clinical and demographic characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Education (years)</th>
<th>Clinical Dementia Rating*</th>
<th>Mini-Mental State Examination</th>
<th>Hamilton Depression Scale</th>
<th>Duration of disease (years)</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>4</td>
<td>1</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>2</td>
<td>69</td>
<td>M</td>
<td>12</td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>1</td>
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<td>3</td>
<td>85</td>
<td>F</td>
<td>4</td>
<td>2</td>
<td>13</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>F</td>
<td>8</td>
<td>1</td>
<td>15</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>F</td>
<td>16</td>
<td>3</td>
<td>13</td>
<td>6</td>
<td>2</td>
<td>1</td>
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<tr>
<td>6</td>
<td>70</td>
<td>F</td>
<td>4</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>1</td>
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<tr>
<td>7</td>
<td>72</td>
<td>F</td>
<td>4</td>
<td>3</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
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<tr>
<td>8</td>
<td>80</td>
<td>F</td>
<td>8</td>
<td>3</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>M</td>
<td>16</td>
<td>1</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>10</td>
<td>89</td>
<td>M</td>
<td>11</td>
<td>1</td>
<td>25</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean (SD) 79.1 (8.6) 65/35 8.7 (8.9) 1.7 (0.8) 17.0 (4.9) 3.0 (2.9) 4.5 (2.2)

*Index as described by Montani and Reines [10]: 0: normal; 0.5: questionable; 1: mild; 2: moderate; 3: severe.

The medication column of this table reports neuroactive medications only. Other medications such as for hypertension and heart disease are not indicated in this table. The point is that, besides the diagnosis of Alzheimer disease, some of these patients were not taking anticholinergic drugs. This is a result of difficult access to these drugs by some patients due to increased costs.

2 mA, 30 min (cephalic reference)

L DLPFC vs L temporal cortex vs sham

Tasks (during stimulation)

- Stroop
- Digit Span
- Visual Recognition Memory task (VRM)

A VRM-correct responses

B VRM-individual performance

Boggio et al, JNNP 2009
atDCS in patients with Alzheimer’s Disease
multiple sessions and sustained effects

15 AD patients within-subject

2 mA, 30 min (bitemporal; extracephalic reference)
Tasks (at T0, T1, T2, T3)
- Encoding and Recognition sequences of VRM
- Visual attention task
- MMSE
- ADAS-COG

Boggio et al, Brain Stim 2012
atDCS in patients with Mild Cognitive Impairment

semantic word generation, task-related activity (fMRI)

Meinzer et al, J Vis Exp 2014

Mean beta values

MCI sham  MCI anodal  Old sham

Meinzer et al, submitted
Summary and outlook
atDCS in MCI and AD patients

- First beneficial effects of atDCS on recognition memory and semantic word generation
- Mechanisms? Increased neuronal efficacy: Decrease in BOLD-activity AND increase in behavioral scores (*Meinzer et al submitted*)

- Future studies
Combination of cognitive training with atDCS over several sessions, outcome parameter closer to IADL (instrumental activities of daily living), follow-up at least 3-6 months
Learning enhancement in patients with post-stroke deficits?
Interhemispheric equilibrium

adapted from Flöel et al, Ann Neurol 2004,
Schlag et al, Arch Neurol 2008
Interhemispheric dysequilibrium

→ dysbalance between hemispheres after unilateral stroke

Interhemispheric dysequilibrium

adapted from Flöel et al, Ann Neurol 2004,
Schlaug et al, Arch Neurol 2008
Interhemispheric dysequilibrium

anodal tDCS?

atDCS in post-stroke aphasia

*mild deficits: over lesioned hemisphere*
atDCS in post-stroke aphasia
mild deficits: over lesioned hemisphere

20 min, 1mA anodal

Fridriksson et al, Cer Cortex 2010

Table 3. Coordinates and Location of Voxels With the Highest Z-Scores Associated With Correct Naming/Location of the Anode Electrode

<table>
<thead>
<tr>
<th>Patient</th>
<th>x*</th>
<th>y*</th>
<th>z*</th>
<th>Location</th>
<th>BA</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>−39</td>
<td>−15</td>
<td>60</td>
<td>Precentral gyrus</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>−55</td>
<td>−4</td>
<td>12</td>
<td>Precentral gyrus</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>−36</td>
<td>52</td>
<td>−4</td>
<td>Middle frontal gyrus</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>−48</td>
<td>−4</td>
<td>46</td>
<td>Precentral gyrus</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>−44</td>
<td>6</td>
<td>44</td>
<td>Precentral gyrus</td>
<td>6</td>
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<tr>
<td>6</td>
<td>−28</td>
<td>46</td>
<td>14</td>
<td>Middle frontal gyrus</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>−54</td>
<td>20</td>
<td>10</td>
<td>Inferior frontal gyrus</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>−12</td>
<td>46</td>
<td>30</td>
<td>Superior frontal gyrus</td>
<td>9</td>
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<tr>
<td>9</td>
<td>−52</td>
<td>16</td>
<td>16</td>
<td>Inferior frontal gyrus</td>
<td>44</td>
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<tr>
<td>10</td>
<td>−60</td>
<td>2</td>
<td>12</td>
<td>Precentral gyrus</td>
<td>6</td>
</tr>
</tbody>
</table>
atDCS in post-stroke aphasia
mild deficits: over lesioned hemisphere

Table 4. Change in the Number of Correctly Named Treated and Untreated Items Between Posttreatment Testing and Baseline Testing After A-IDCS and S-IDCS

<table>
<thead>
<tr>
<th>Patient</th>
<th>A-IDCS</th>
<th>S-IDCS</th>
<th>A-IDCS</th>
<th>S-IDCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated Items</td>
<td>Treated Items</td>
<td>Untreated Items</td>
<td>Untreated Items</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0</td>
<td>17</td>
<td>-2</td>
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<tr>
<td>2</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>1</td>
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<tr>
<td>3</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>-1</td>
</tr>
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<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
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<td>0</td>
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<tr>
<td>7</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>8</td>
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<td>-1</td>
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<tr>
<td>9</td>
<td>3</td>
<td>-3</td>
<td>-1</td>
<td>2</td>
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<tr>
<td>10</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>15</td>
<td>40</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>1 Week Posttreatment - Baseline</th>
<th>A-IDCS</th>
<th>S-IDCS</th>
<th>A-IDCS</th>
<th>S-IDCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated Items</td>
<td>Treated Items</td>
<td>Untreated Items</td>
<td>Untreated Items</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0</td>
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<td>4</td>
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<td>0</td>
<td>1</td>
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<td>5</td>
<td>6</td>
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<tr>
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<td>0</td>
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<tr>
<td>Total</td>
<td>35</td>
<td>11</td>
<td>42</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Correlation Matrix for Treatment Outcome (Change Scores) and Biographical Information

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Education, y</th>
<th>Poststroke Onset, mo</th>
<th>Lesion Size, cm^3</th>
<th>Aphasia Severity</th>
<th>AOS Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Items</td>
<td>-0.613</td>
<td>-0.152</td>
<td>-0.182</td>
<td>-0.039</td>
<td>0.126</td>
</tr>
<tr>
<td>untreated Items</td>
<td>-0.402</td>
<td>-0.175</td>
<td>-0.043</td>
<td>-0.049</td>
<td>0.252</td>
</tr>
<tr>
<td>Total Items</td>
<td>-0.535</td>
<td>-0.186</td>
<td>-0.105</td>
<td>-0.048</td>
<td>0.229</td>
</tr>
</tbody>
</table>

AOS indicates apraxia of speech.
None of the relations reached significance (P<0.05).
*Measured by the Aphasia Quotient from the Western Aphasia Battery-Revised.
†Measured by subtest 6 from the Apraxia Battery for Adults-Second Edition.
‡Treated and untreated items combined.

Baker et al, Stroke 2010
atDCS in post-stroke aphasia

*moderate to severe deficits: over non-lesioned hemisphere*
atDSC in post-stroke aphasia

*moderate to severe deficits: over non-lesioned hemisphere*

**Combined behavioral-fMRI**

→ Which brain areas have to be re-activated for successful naming

in moderate to severe chronic aphasia?

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*Menke et al, BMC Neurosci 2009*
atDCS in post-stroke aphasia
moderate to severe deficits: over non-lesioned hemisphere

Floel et al, Stroke 2011
Summary and outlook
post-stroke aphasia

- Intensive naming training leads to highly significant improvements
  *Left-hemispheric atDCS* → *significant increase in naming ability in mild aphasia*
  *Right-hemispheric atDCS* → *significant increase in naming ability in moderate to severe aphasia*

- Outcomes measures focused on disability and participation, eg Amsterdam-Nijmegen Every Day Language Test
- Long-term follow-up (6-12 months)
- Direct comparison of different modes of stimulation

→ Multi-center RCT, combining
  - *language training* (eg, using an intensive training based on function-specific and participation-oriented training as used in FET2EC-trial *(Breitenstein et al, ongoing)* or constrained-induced aphasia therapy *(Pulvermüller et al, Stroke 2001)*)
  - *atDCS with pre-defined site for electrodes*
Future directions for tDCS in Clinical Disorders

- **Post-stroke deficits, MCI/AD**
  → Establish clinical relevance of specific tDCS protocols in RCTs in patients using appropriate outcome measures (not only „function“ but also measures of activities and participation)
  → long-term follow-up
  → define characteristics of „responders“, develop novel protocols for „non-responders“

- **Movement disorders, epilepsy, and others**
  → Optimization of stimulation protocols (intensity, duration, repetition intervals, number of stimulation session) in patient populations, using neurophysiology and behavioral outcomes in pilot studies
  → then move on to RCTs as described above

Thanks for your attention!