CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

HBM Educational course

„Brain Stimulation: Past, Present and Future“

Hamburg, June 8th, 2014

tDCS in Clinical Disorders

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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

NeuroImage 85 (2014) 934–947

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

tDCS-enhanced motor and cognitive function in neurological diseases

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NeuroImage 85 (2014) 948–960

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

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

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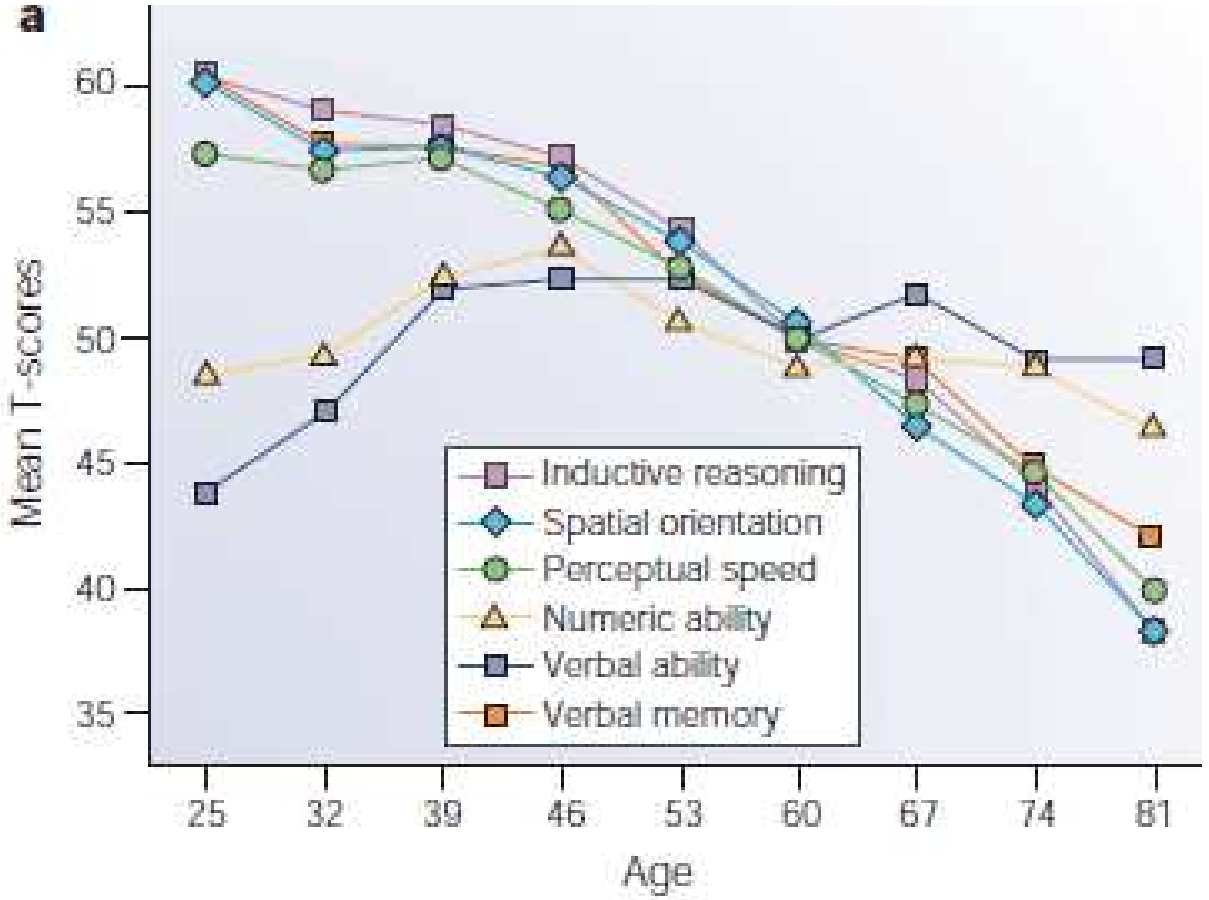
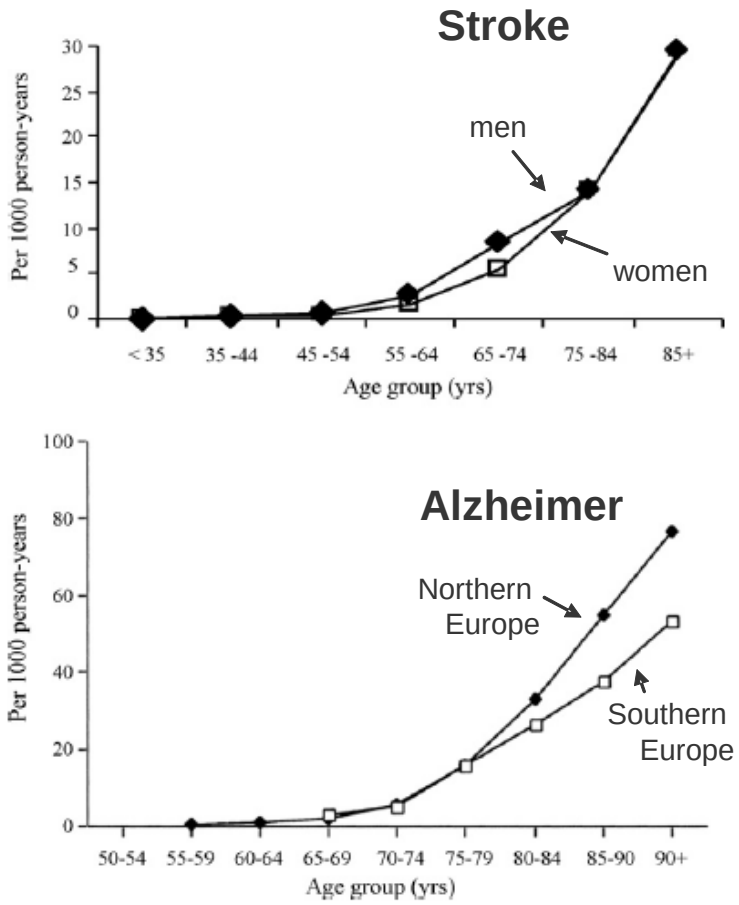
Cognitive functions over the lifespan

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

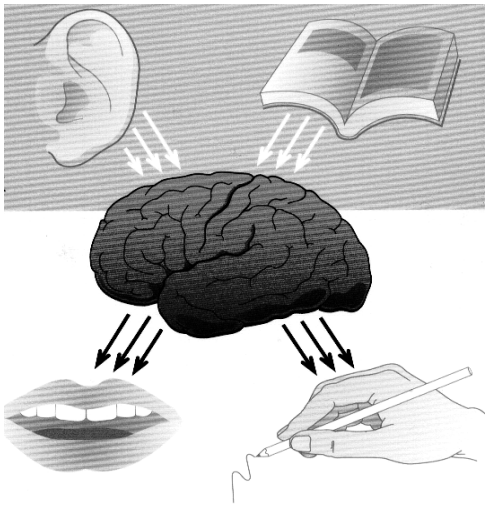
- Memory complaint
- Memory and at least one other cognitive domain impaired
- Impaired activities of daily living

→core symptoms: deficits in learning and memory formation

Enhanced learning success by means of adjuvant interventions?

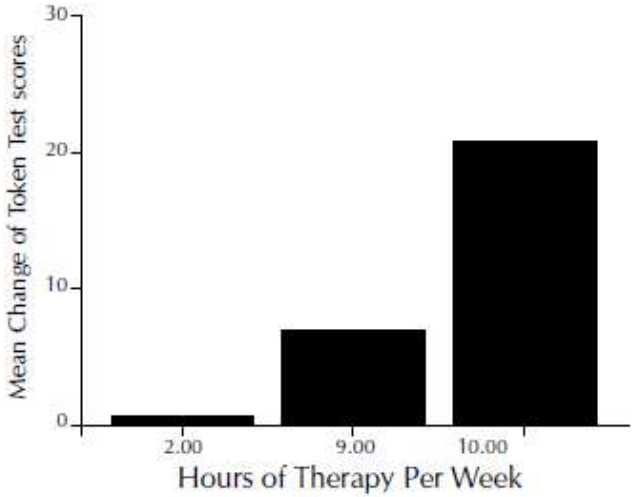
Post-stroke aphasia

20 % of surviving stroke patients
→ permanent deficits in language function



Pedersen et al, Ann Neurol 2004

Training in chronic strage of aphasia?
→ at least 9 hours/week needed

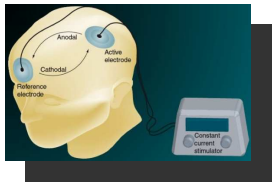


Bhogal et al., 2003 Stroke

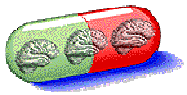
Enhanced training success by means of adjuvant interventions?

Adjuvant interventions to increase learning ability „neuroplasticity“ in neurological and psychiatric disorders

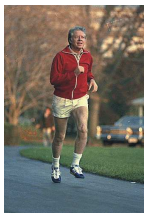
- Non-invasive brain stimulation
  - repetitive transcranial magnetic stimulation (rTMS)
  - transcranial direct current stimulation (tDCS)
  - …



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

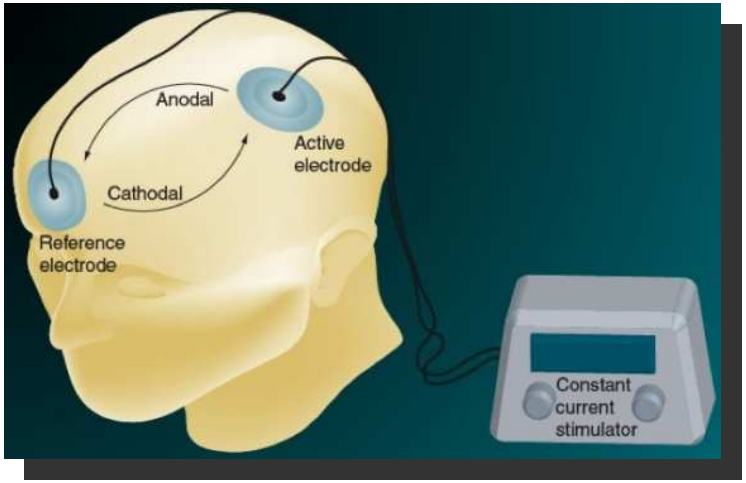


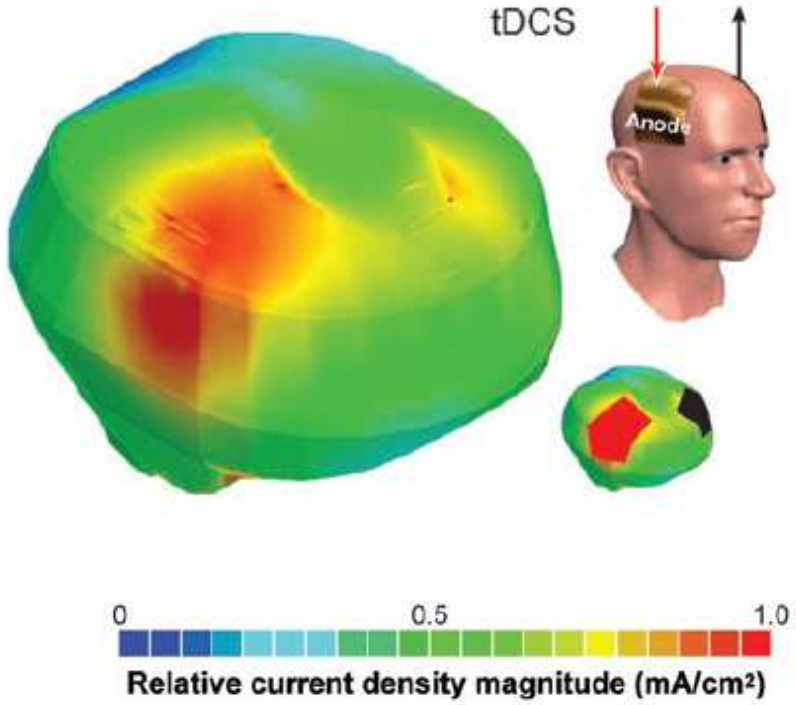
- Endogenous learning modulation
  - physical activity
  - dietary factors
  - …



Non-invasive brain stimulation

Transcranial direct current stimulation, tDCS

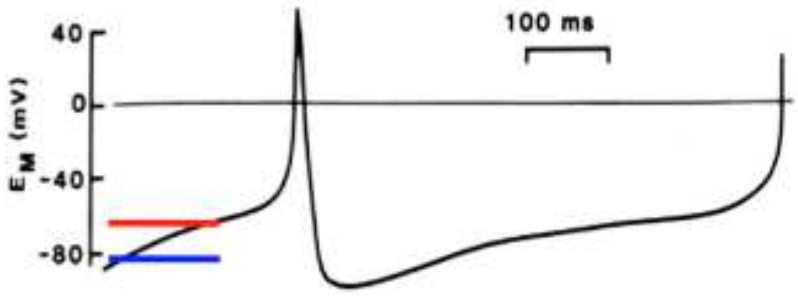




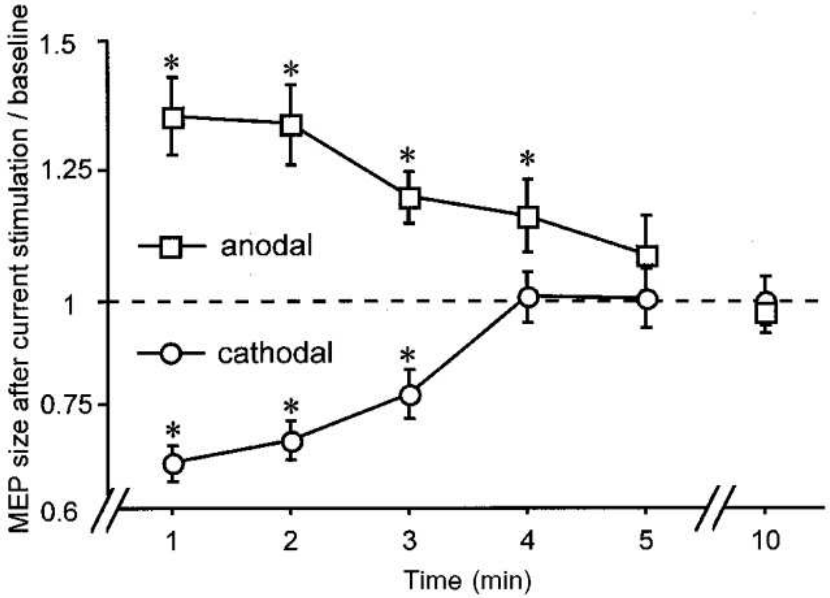
Wagner et al, Ann Rev Biomed Eng 2007

tDCS

Modulation of resting membrane potential



courtesy by M. Nitsche, Göttingen



Nitsche et al, J Physiol 2000

- **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 (eg motor training)**
- **Possible to blind participants and person applying stimulation** *(Stagg and Nitsche, Neuroscientist 2011)*

tDCS in patient studies

Easy Applicability, Safety & Comfort

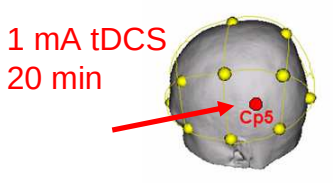
	tDCS	rTMS
Quality of sensations (Anand and Hotson, 2002; Hummel *et al.*, 2005a; Paulus, 2003)	No sound, mild transient tingling sensations, no twitches	Sound, tingling, muscle twitch under the coil if suprathreshold
Duration of sensation (Anand and Hotson, 2002; Hummel *et al.*, 2005a; Paulus, 2003)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

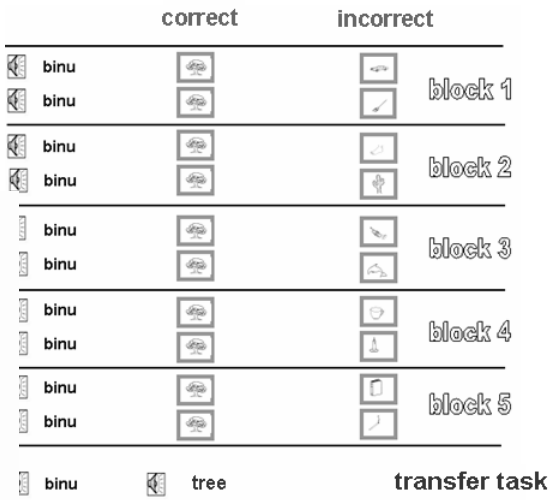
Gandiga et al, Clin Neurophysio 2006

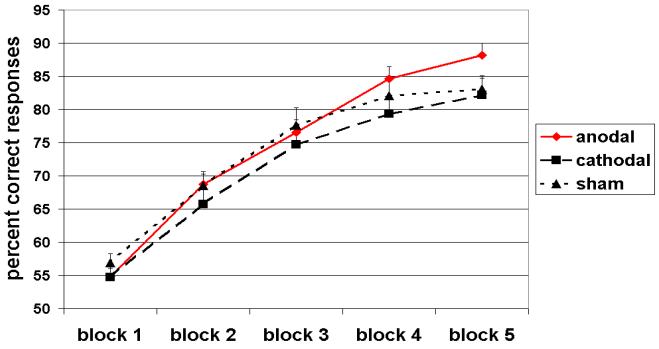
Learning improvement

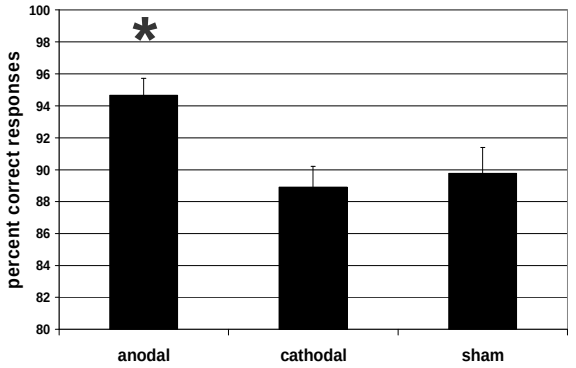
atDCS

Learning of a novel vocabulary, single session



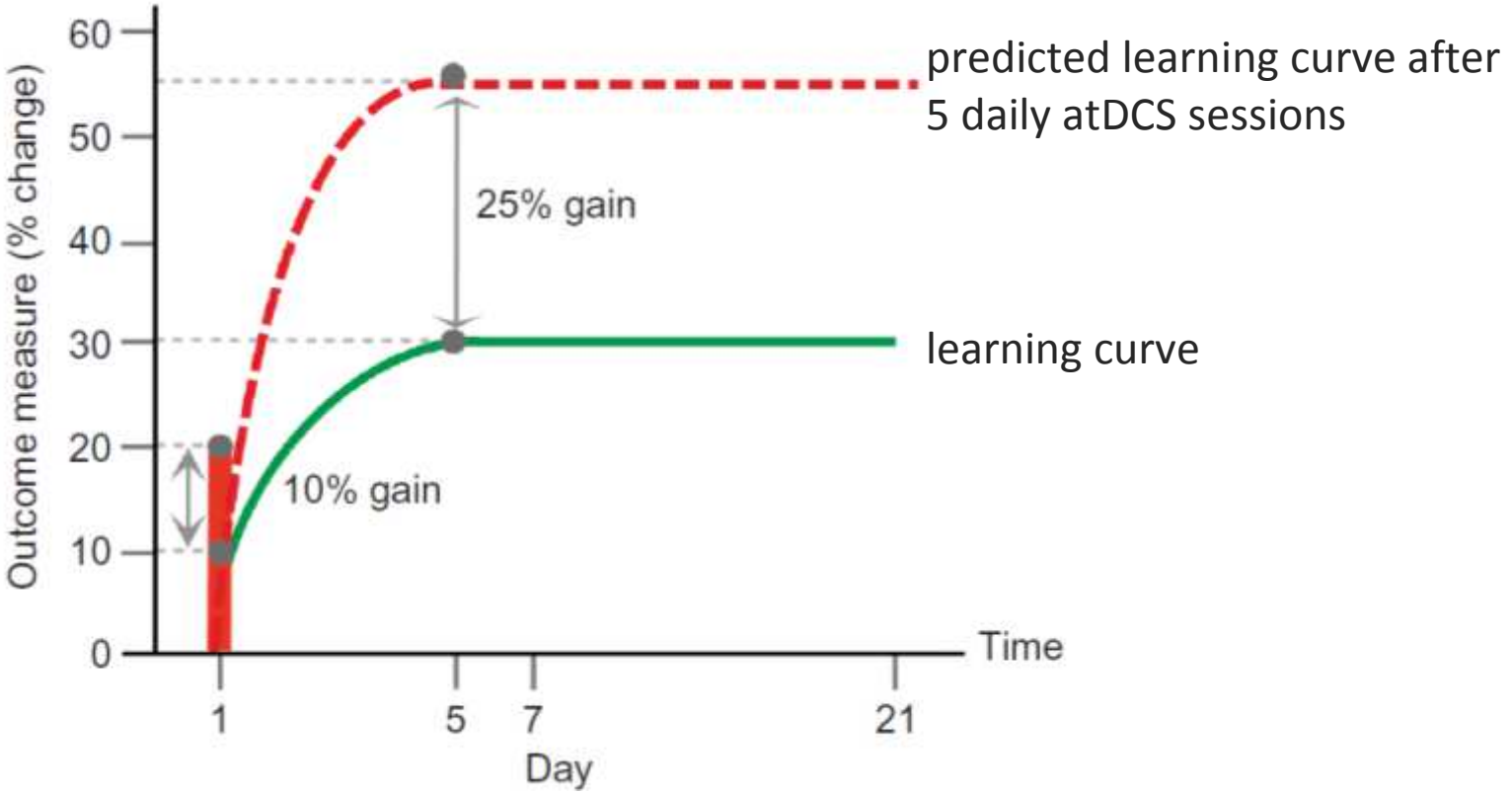






Flöel et al, J Cogn Neurosci 2008
see also Fiori et al, J Cogn Neurosci 2010

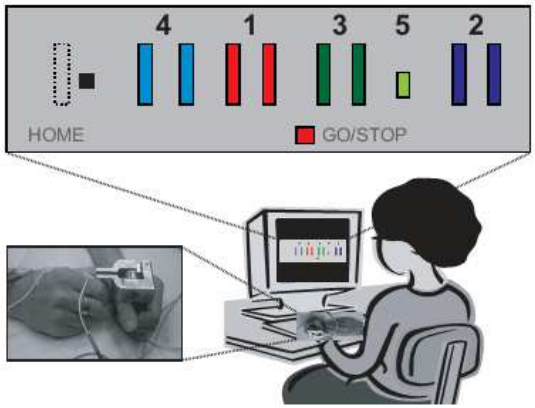
Does atDCS lead to sustained gains in learning?

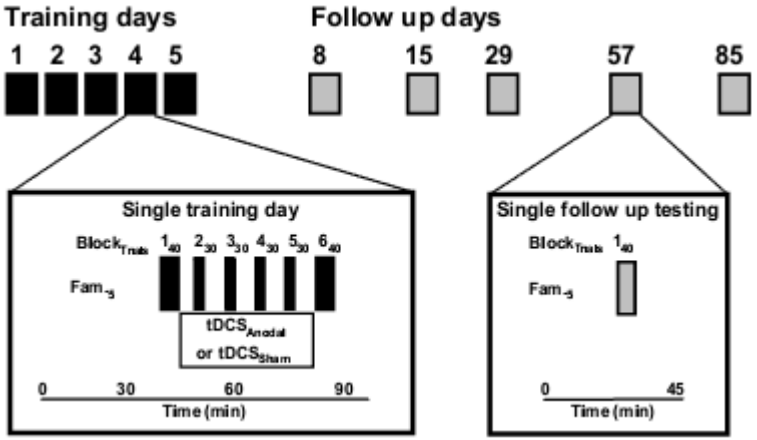


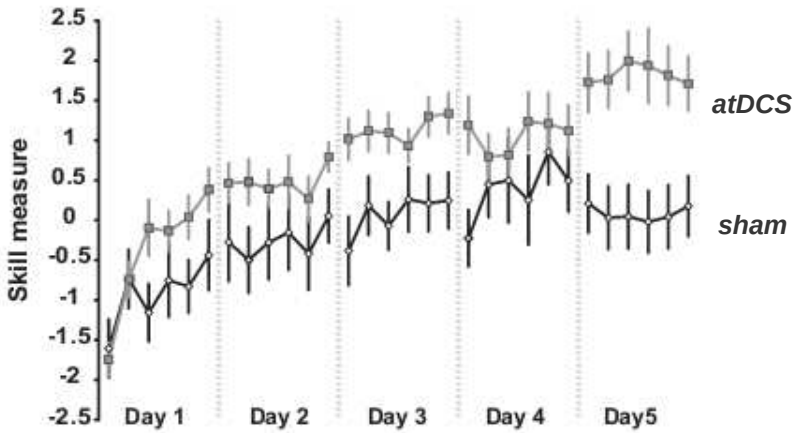
Holland and Crinion, Aphasiology 2011

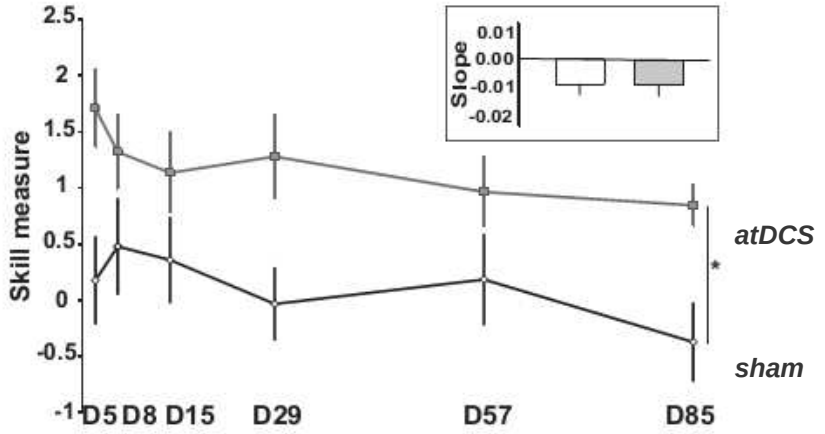
atDCS

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

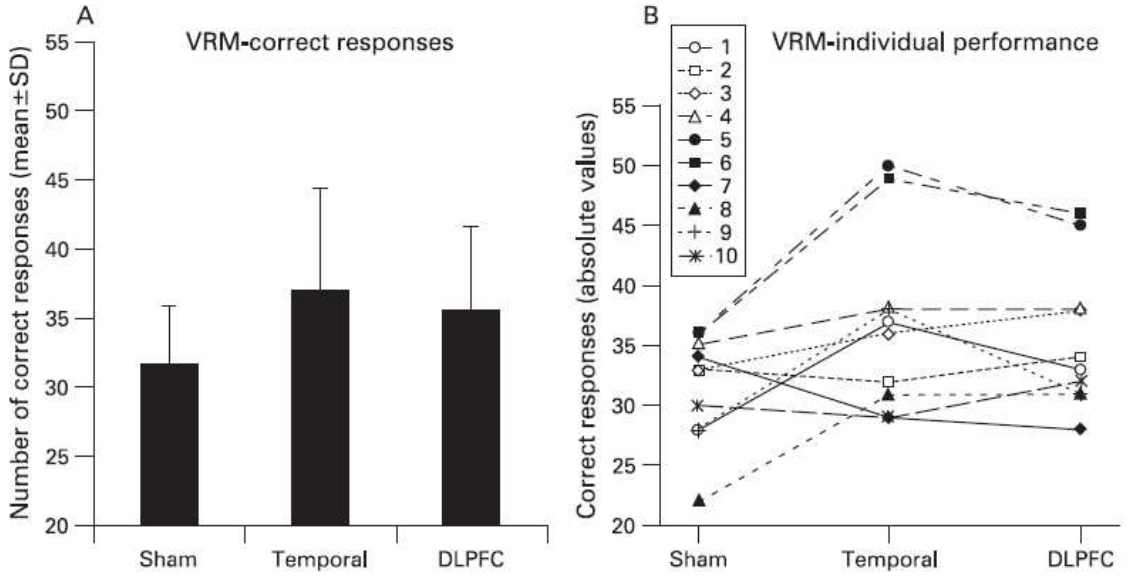
single-session

Table 1 Clinical and demographic characteristics

Subjects	Age (years)	Gender	Education (years)	Clinical Dementia Rating*	Mini-Mental State Examination	Hamilton Depression Scale	Duration of disease (years)	Medication
1	74	M	4	1	22	2	4	†
2	69	M	12	1	20	2	6	Pimozide, Bromazepam, Periciazine
3	85	F	4	2	12	1	6	†
4	92	F	8	1	13	0	9	Hydergine
5	88	F	16	1	15	7	5	†
6	70	F	4	3	13	6	2	Imipramine, Haloperidol, Clonazepam
7	72	F	4	3	14	0	2	Galantamine, Sertraline
8	80	F	8	3	13	8	4	Rivastigmine, Olanzapine
9	72	M	16	1	23	2	2	Clonazepam
10	89	M	11	1	25	2	5	Periciazine, Fluoxetine
Mean (SD)	79.1 (8.8)	6F/4M	8.7 (4.9)	1.7 (0.9)	17.0 (4.9)	3.0 (2.9)	4.5 (2.2)	

*Index as described by Montanõ and Ramos [16]: 0, normal; 0.5, questionable; 1, mild; 2, moderate; 3, severe.
†The medication column of this table reports neuropsychoactive medications only. Other medications such as for hypertension and heart disease are not indicated in this table. One point is that, besides the diagnostic 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 elevated costs.

2 mA, 30 min (cephalic reference)
L DLPFC vs L temporal cortex vs sham
Tasks (during stimulation)
- Stroop
- Digit Span
- Visual Recogniton Memory task (VRM)

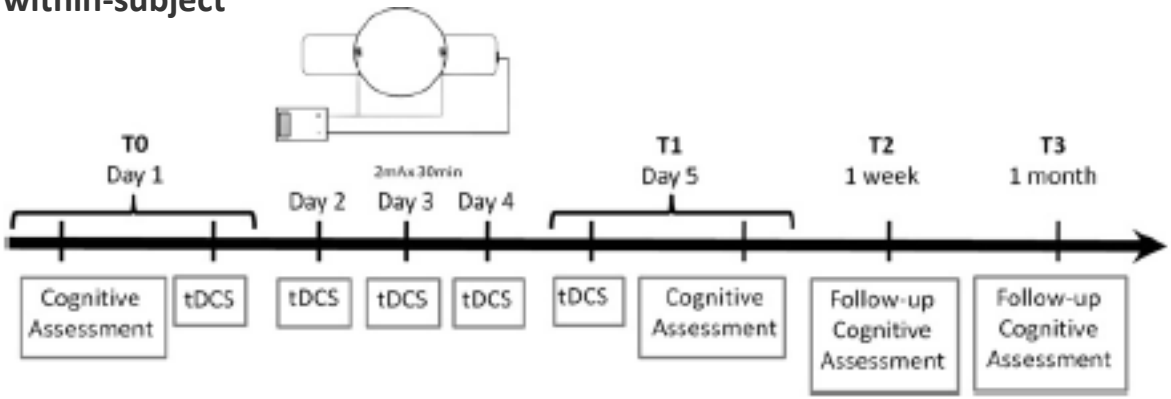


Boggio et al, JNNP 2009

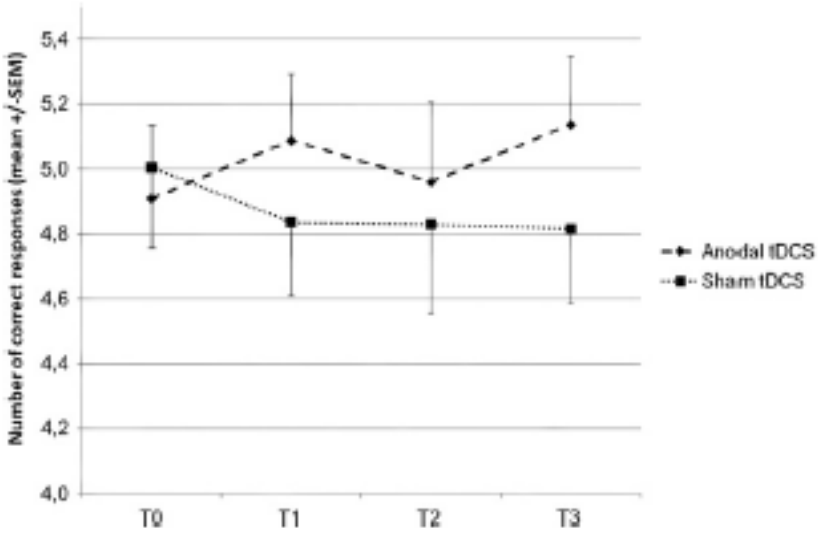
atDCS in patients with Alzheimer‘s Disease

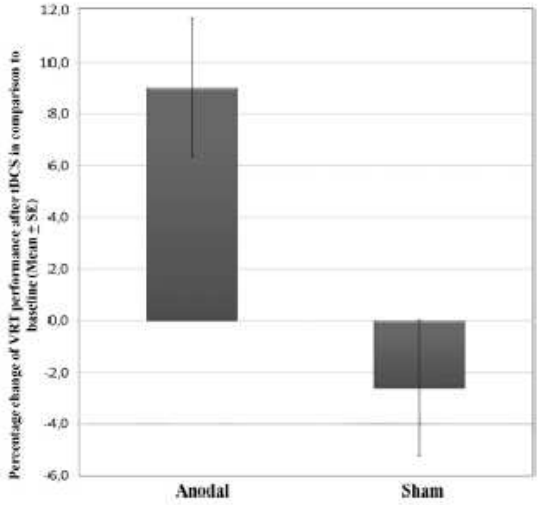
multiple sessions and sustained effects

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

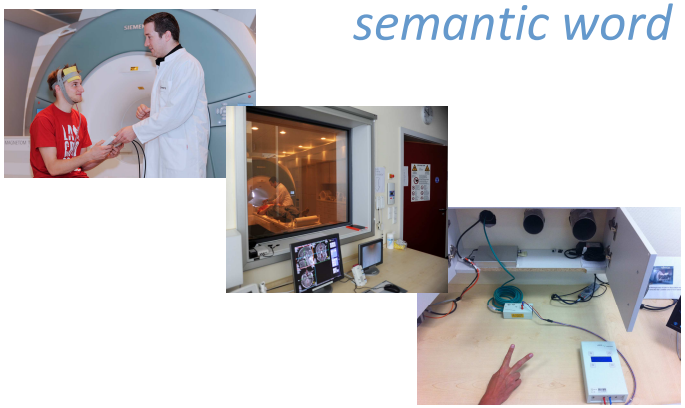




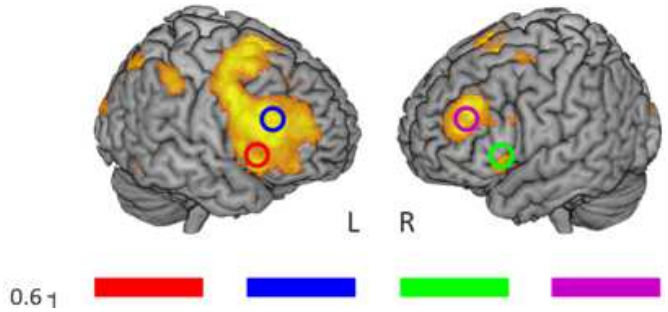
Boggio et al, Brain Stim 2012

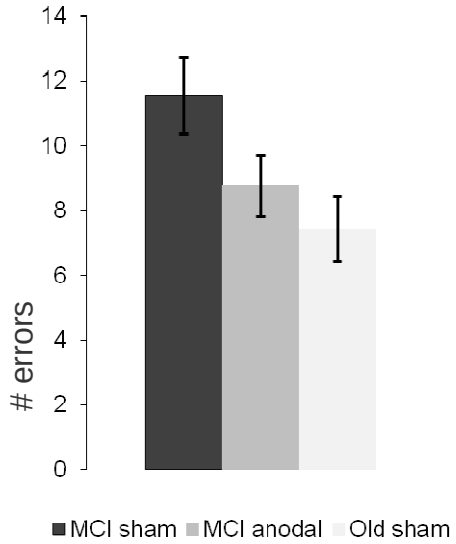
atDCS in patients with Mild Cognitive Impairment

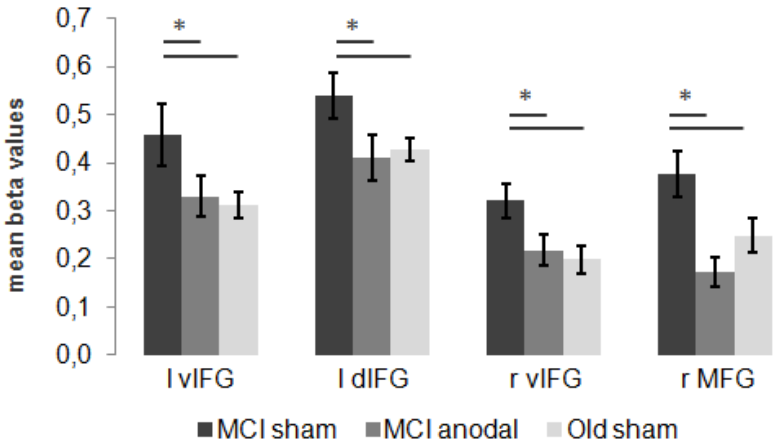
semantic word generation, task-related activity (fMRI)



Meinzer et al, J Vis Exp 2014







Meinzer et al, submitted

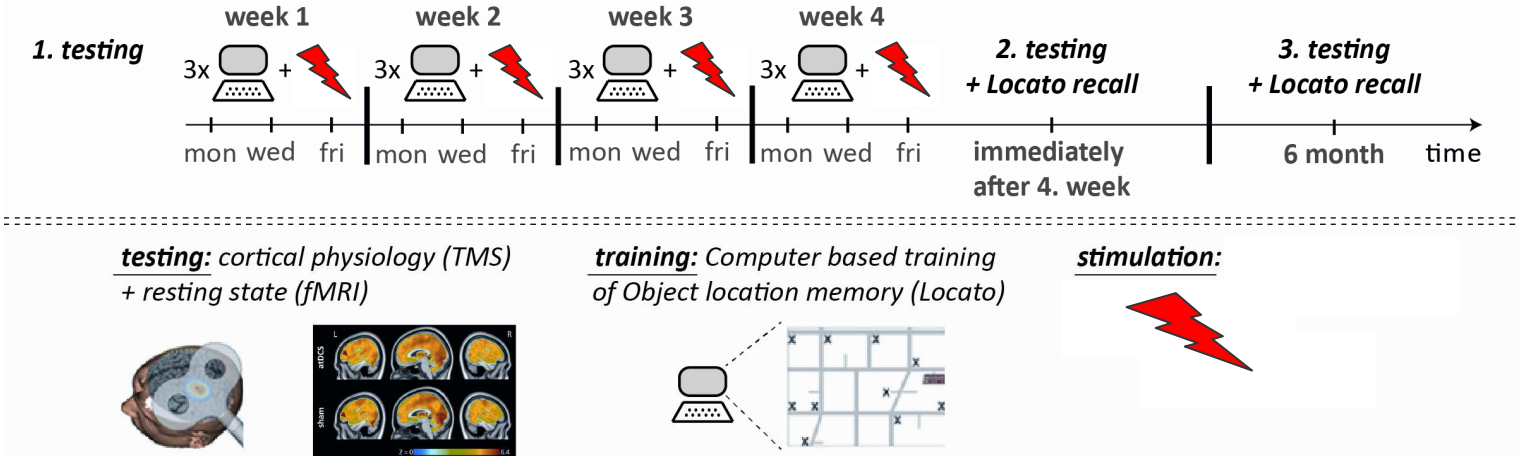
Summary and outlook

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)*

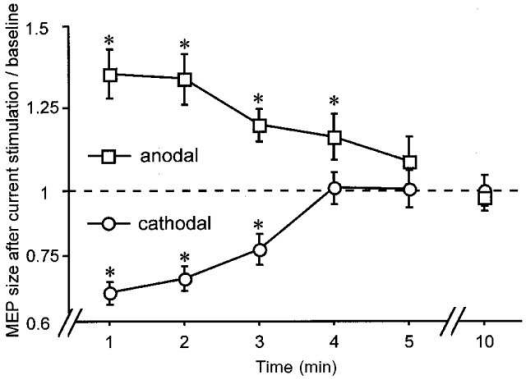
- Future studies

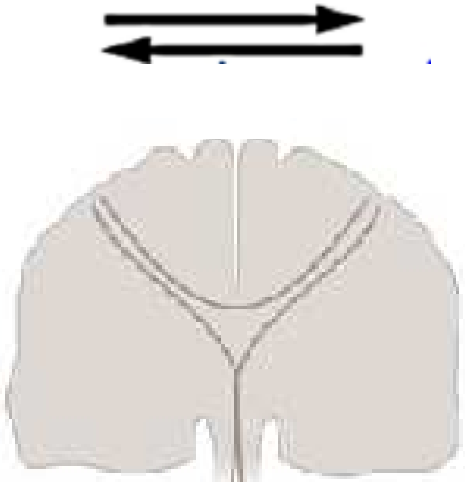
Combination of cognitive training with atDCS over several sessions, outcome parameter closter to IADL (instrumental activities of daily living), follow-up at least 3-6 months



Learning enhancement in patients with post-stroke deficits?

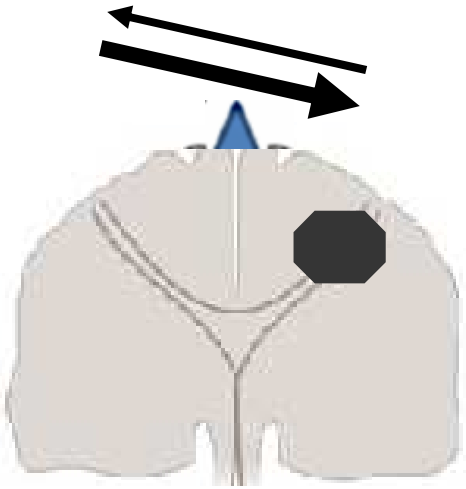
Interhemispheric equilibrium





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

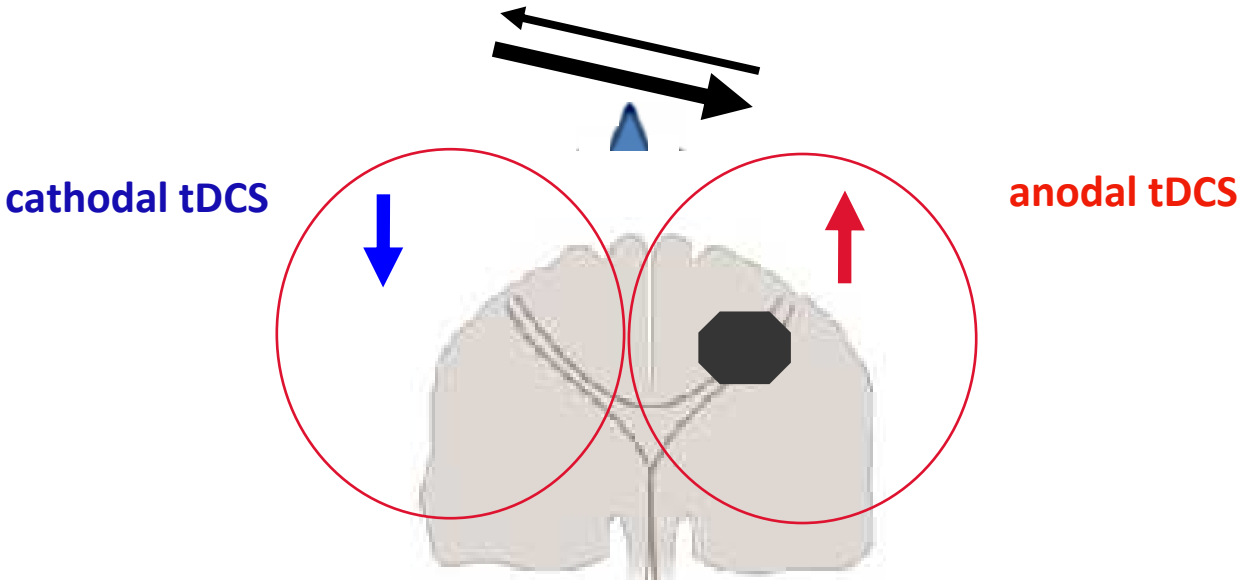
Interhemispheric dysequilibrium



→ dysbalance between hemispheres after unilateral stroke

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

Interhemispheric dysequilibrium



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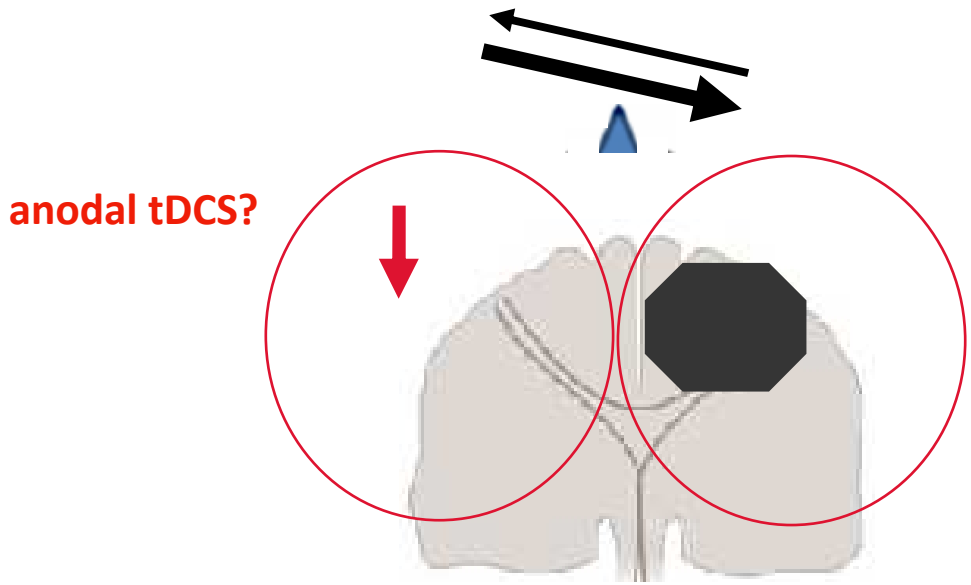
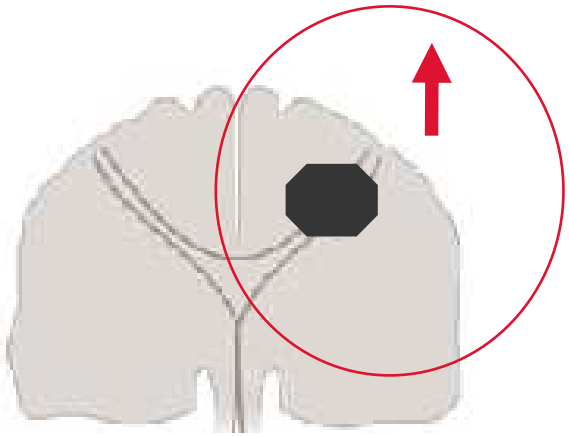
Interhemispheric dysequilibrium



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

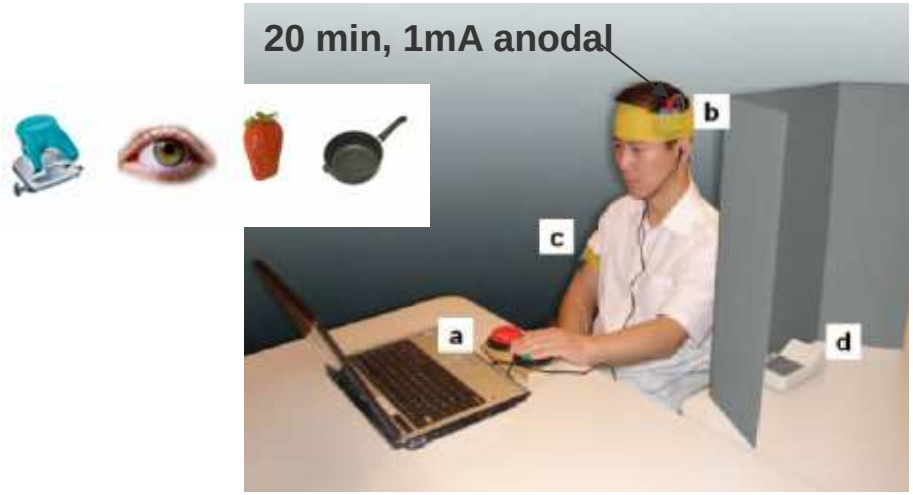
atDCS in post-stroke aphasia

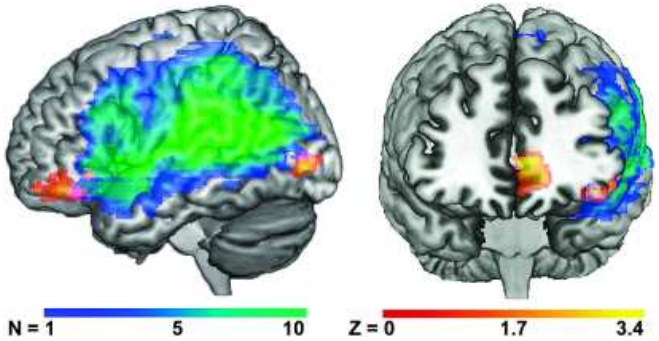
mild deficits: over lesioned hemisphere



atDCS in post-stroke aphasia

mild deficits: over lesioned hemisphere





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

Patient	*x**	*y**	*z**	Location†	BA
1	−39	−15	60	Precentral gyrus	6
2	−55	−4	12	Precentral gyrus	6
3	−36	52	−4	Middle frontal gyrus	10
4	−48	−4	46	Precentral gyrus	6
5	−44	6	44	Precentral gyrus	6
6	−28	46	14	Middle frontal gyrus	46
7	−54	20	10	Inferior frontal gyrus	45
8	−12	46	30	Superior frontal gyrus	9
9	−52	16	16	Inferior frontal gyrus	44
10	−60	2	12	Precentral gyrus	6

Baker et al, Stroke 2010

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-tDCS and S-tDCS

	Immediate Posttreatment >Baseline				1 Week Posttreatment >Baseline			
Patient	A-tDCS Treated Items	S-tDCS Treated Items	A-tDCS Untreated Items	S-tDCS Untreated Items	A-tDCS Treated Items	S-tDCS Treated Items	A-tDCS Untreated Items	S-tDCS Untreated Items
1	5	0	17	−2	8	−2	10	1
2	5	4	6	1	3	2	9	−1
3	10	10	3	−1	5	5	5	0
4	1	0	1	2	1	0	1	2
5	6	0	6	−1	6	−2	2	0
6	0	0	0	0	0	0	0	0
7	1	1	1	1	1	0	1	−1
8	2	2	2	−1	3	0	3	−1
9	3	−3	−1	2	5	2	1	6
10	3	1	5	2	3	6	10	9
Total	36	15	40	3	35	11	42	15

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

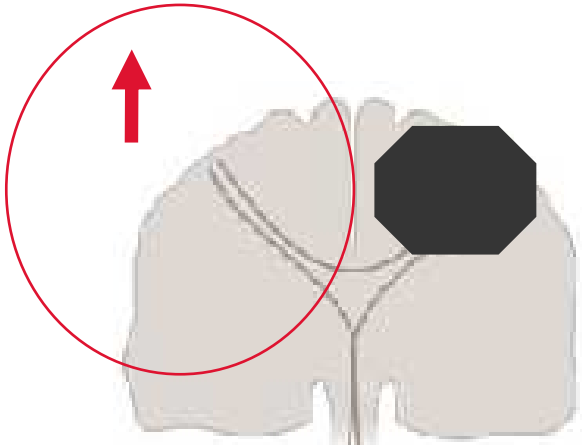
	Age, y	Education, y	Poststroke Onset, mo	Lesion Size, cm^3	Aphasia Severity*	AOS Severity†
Treated items	−0.613	−0.152	−0.182	−0.030	0.126	0.306
Untreated items	−0.402	−0.175	−0.043	−0.049	0.252	0.233
Total items‡	−0.535	−0.186	−0.105	−0.048	0.229	0.290

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

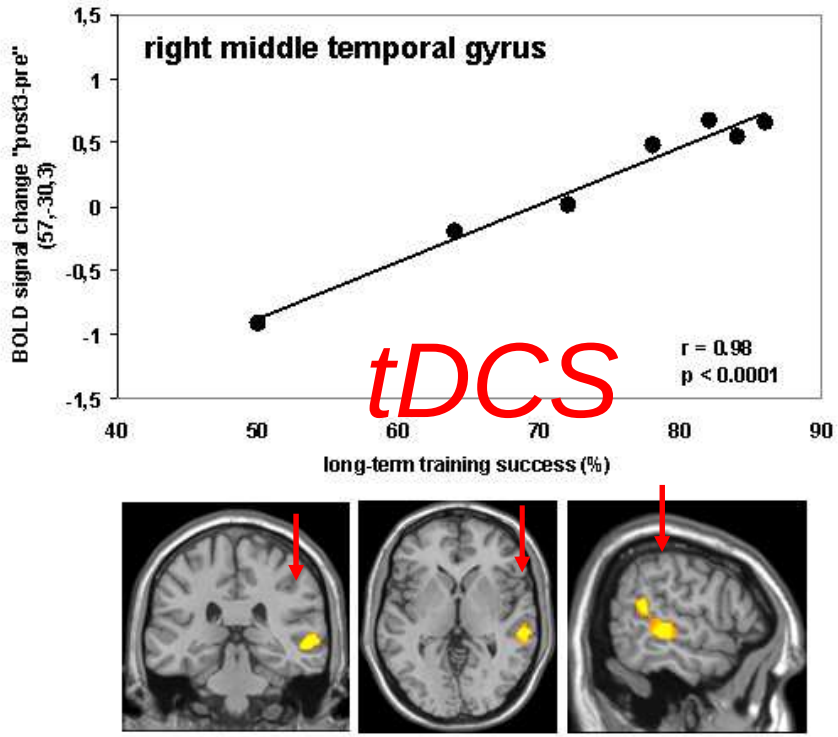


atDCS in post-stroke aphasia

moderate to severe deficits: over non-lesioned hemisphere

Combined behavioral-fMRI

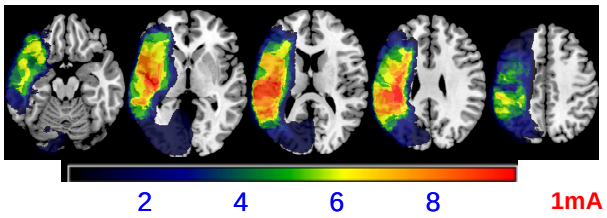
→ Which brain areas have to be re-activated for successful naming in moderate to severe chronic aphasia?

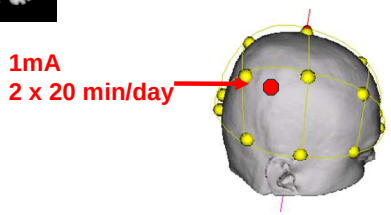


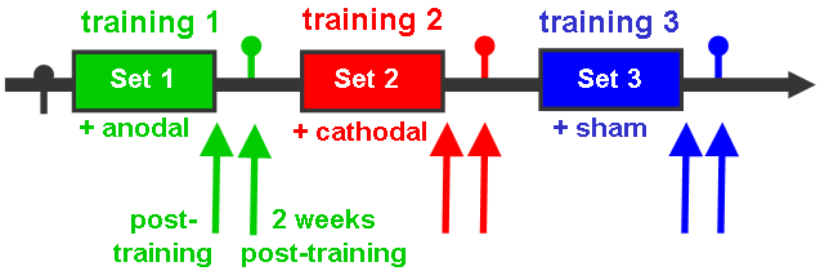
Menke et al, BMC Neurosci 2009

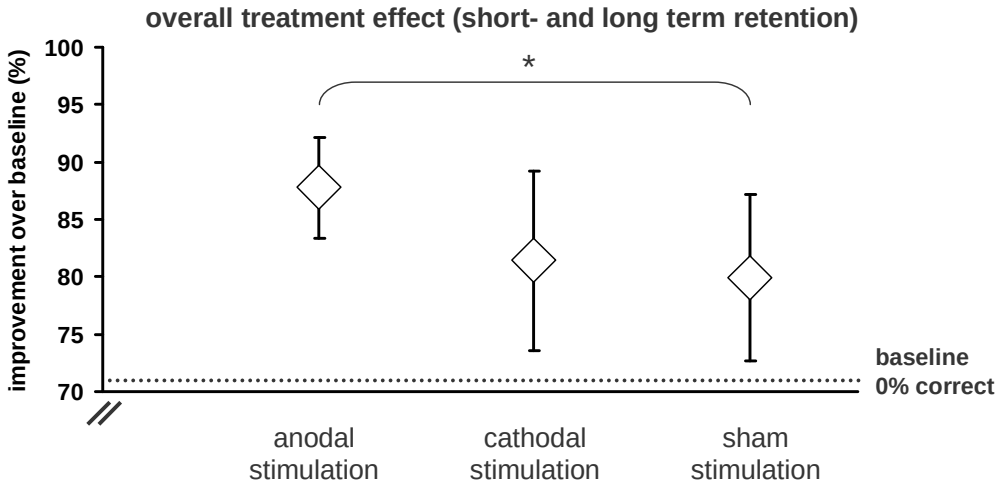
atDCS in post-stroke aphasia

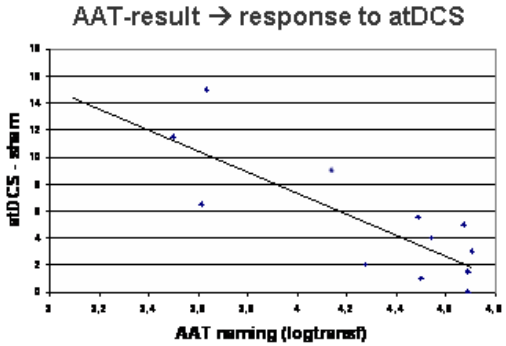
moderate to severe deficits: over non-lesioned hemisphere











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!