Recovery mechanisms from aphasia

Dr. Michal Ben-Shachar

977 Acquired language and reading impairments
Research questions

- Which brain systems can support recovery from aphasia?
- Which compensatory route leads to better functioning?
- What is the time course of recovery after stroke?
Clinical question

- How can we assist recovery in the most efficient and effective way?
- How can we speed up the timeline of recovery?
Dynamics of language reorganization after stroke

Dorothee Saur,¹ Rüdiger Lange,¹ Annette Baumgaertner,² Valeska Schraknepper,³ Klaus Willmes,⁴ Michel Rijntjes¹ and Cornelius Weiller¹

¹Department of Neurology, University Freiburg, Freiburg, ²NeuroImage Nord, ³Department of Neurology, University Medical Centre Hamburg-Eppendorf, Hamburg and ⁴Section Neuropsychology, Department of Neurology, RWTH Aachen University, Aachen, Germany
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Previous functional imaging studies of chronic stroke patients with aphasia suggest that recovery of language occurs in a pre-existing, bilateral network with an upregulation of undamaged areas and a recruitment of perilesional tissue and homologue right language areas. The present study aimed at identifying the dynamics of reorganization in the language system by repeated functional MRI (fMRI) examinations with parallel language testing from the acute to the chronic stage. We examined 14 patients with aphasia due to an infarction of the left middle cerebral artery territory and an age-matched control group with an auditory comprehension task in an event-related design. Control subjects were scanned once, whereas patients were scanned repeatedly at three consecutive dates. All patients recovered clinically as shown by a set of aphasia tests. In the acute phase [mean: 1.8 days post-stroke (dps)], patients’ group analysis showed little early activation of non-infarcted left-hemispheric language structures, while in the subacute phase (mean: 12.1 dps) a large increase of activation in the bilateral language network with peak activation in the right Broca-homologue (BHo) was observed. A direct comparison of both examinations revealed the strongest increase of activation in the right BHo and supplementary motor area (SMA). These upregulated areas also showed the strongest correlation between improved language function and increased activation ($r_{BHo} = 0.88, r_{SMA} = 0.92$). In the chronic phase (mean: 321 dps), a normalization of activation with a re-shift of peak activation to left-hemispheric language areas was observed, associated with further language improvement. The data suggest that brain reorganization during language recovery proceeds in three phases: a strongly reduced activation of remaining left language areas in the acute phase is followed by an upregulation with recruitment of homologue language zones, which correlates with language improvement. Thereafter, a normalization of activation is observed, possibly reflecting consolidation in the language system.
Fig. 1 Site of infarction of 14 patients. Axial diffusion-weighted MRI scans at the level of maximum infarct volume for each aphasic patient. Left side of the figure corresponds to the left side of the brain.
Behavioural evaluation

It is almost impossible to use a single standardized aphasia test throughout the entire course of aphasia recovery; therefore, our aphasia test battery, which was administered at each time of MRI scanning, consisted of tests for both acute and chronic aphasia: (i) the AABT (Biniek et al., 1992); (ii) the subtests repetition, written language, naming and auditory and reading comprehension of the AAT (Huber et al., 1984); (iii) the Token Test (TT) subtest of the AAT; (iv) an analysis of spontaneous speech (SPS); and (v) the Communicative Effectiveness Index (CETI; Lomas et al., 1989). Scores within each of these five assessments were summarized, respectively. In compiling the scores, the TT score was converted such that high scores reflected correct performance, by subtracting the obtained error score from the maximum error score possible for the TT. For an analysis of SPS, we recorded a semi-standardized interview, which was analysed according to the AAT criteria of communicative abilities, articulation and prosody, automated speech, semantic, phonemic and syntactic structure. Task performance in the scanner contributed as a separate language score (see language paradigm for details). Thus, there was a set of six language measures for each patient at each examination. These scores were normalized to a range of 0–1 ($\text{score}_{\text{nor}}$) and averaged into a composite score labelled the ‘overall language recovery score’ $\text{LRS} = \lfloor \text{AABT}_{\text{nor}} + \text{AAT \ (without TT and SPS}_{\text{nor}}) + \text{TT}_{\text{nor}} + \text{SPS}_{\text{nor}} + \text{CETI}_{\text{nor}} + \text{Task}_{\text{nor}} \rfloor / 6$ with a resulting range between 0 and 1. The LRS was taken to be a reasonable univariate index of overall level of language performance at any given time for later correlation with activation patterns (see imaging analysis).
Behavioral recovery

Fig. 2 Individual and mean Language Recovery Curves of 14 patients. (A) Plots of normalized overall LRS for each patient across three sessions. Each patient had six separate language performance scores recorded at each fMRI session (comprehension task, AABT, AAT, TT, SP, CETI), creating six specific recovery curves per patient. The overall LRS represents a composite score, by normalizing and averaging the six language performance scores at each time. (B) Mean Language Recovery Curve; asterisk (*) indicates significant improvement (paired t-test, two-tailed).

Ex1: 0-4 days post stroke
Ex2: 2 weeks post stroke
Ex3: 4-12 months post stroke
Activation for sentences > reversed

0-4 days post stroke
2 weeks post stroke
4-12 months post stroke
Behavioral change predicts activation change

Fig. 4 Correlation of initial impairment and language activation (A) and early improvement and increase of language activation (B). A: Results of the simple regression analysis of initial language impairment (LRS_{Ex1}) and language activation (contrast image = [1 1 1 -1 -1]). All voxels are significant at $P < 0.001$ (uncorrected for multiple comparisons, $t > 3.93$). At $[-57 15 -9]$, peak is located in infarcted tissue in three patients (marked with filled claver). B: Results of the simple regression analysis of early language improvement (LRS_{Ex2/Ex1}) and increase of activation (contrast image = [-1 -1 1 1 1 -1 -1 -1]). All voxels are significant at $P < 0.001$ (uncorrected for multiple comparisons, $t > 3.93$).
Fig. 5 Model with three phases of language recovery after stroke. Three phases of language recovery: Acute Phase I characterized by loss of function; Subacute Phase II by an upregulation of the language network; Chronic Phase III by a consolidation and normalization of activation. Diagrammed activation of controls (—), left language areas (---) and right language areas of aphasic patients (.). Crosses (X) indicate time of fMRI (examinations 1, 2 and 3).
Review

Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation

Roy H. Hamilton\textsuperscript{a,b,*}, Evangelia G. Chrysikou\textsuperscript{c}, Branch Coslett\textsuperscript{a,b}

\textsuperscript{a} University of Pennsylvania, Department of Neurology, Center for Cognitive Neuroscience, Philadelphia, PA, United States
\textsuperscript{b} Laboratory for Cognition and Neural Stimulation, University of Pennsylvania, Philadelphia, PA, United States
\textsuperscript{c} University of Pennsylvania, Department of Psychology, Center for Cognitive Neuroscience, Philadelphia, PA, United States
Aphasic patients activate more bilateral networks (Meta-analysis)
Related results from stuttering: Adults who stutter show increased right frontal activation when listening to speech.

**Speech vs. SCN**
- \( t = 3.40 \)  
- \( p < 0.001 \)

**SCN vs. rest**
- \( t = 3.40 \)  
- \( p < 0.001 \)
Enhanced right frontal activation in adults who stutter when listening to speech

Halag-Milo et al., NICL2016
Is bilaterality a good thing?
It depends…

Current evidence suggests that three kinds of changes in neural activity after stroke may be most relevant for aphasia recovery: (1) Recruitment of lesioned and perilesional left hemisphere regions for language-related tasks, (2) acquisition, unmasking or refinement of language processing ability in the nondominant right hemisphere, and (3) dysfunctional activation of the nondominant hemisphere that may interfere with language recovery. We will

Fig. 2. Differing accounts of plasticity in language systems in chronic aphasia. (a) After unilateral left hemisphere stroke (grey), some language functions may be subserved by recovered lesional areas or recruited perilesional areas (light green). (b) Right perisylvian areas (light green) may be recruited to subserve some language functions, a process facilitated by decreased transcallosal inhibition of the right hemisphere by the damaged left hemisphere. (c) By contrast, right hemisphere activity may be deleterious. Released from interhemispheric inhibition, right hemisphere structures (red) may exert increased inhibitory influence on left perisylvian areas, impeding functional recovery of lesional and perilesional areas in the left hemisphere (dark green).
Proposed mechanism for perilesional compensation (similar to Merzenich’s plasticity experiments)

- Release from inhibition: the impaired left hemisphere region stops responding and therefore does not inhibit the areas around it during language input
- Peri-lesional cortex is active during language input
- Activity Dependent Plasticity: positive feedback links perilesional activity with language and this relation becomes stronger until it is independent of the lesioned area
Contribution of the right hemisphere to recovery

Positive effects:
- Case studies of aphasics who got better and then lost their language by a second, RH stroke
- Wada test shows that injection to the right carotid impairs language in aphasic patients
- Patients who had left hemispherectomy recovered language function – must be through right hemisphere
Proposal: right hemisphere homologous regions to the left language areas can process language but are normally masked by inhibitory callosal connections.

After stroke these latent language abilities are unmasked
Basis for therapy

● The idea that right hemisphere activation can be compensatory provides the basis for techniques that enhance RH activation
  – E.g., MIT
  – Naming + complex left hand movement (Crosson et al)

● It’s possible that right hemi compensation is only temporary, in the subacute stage, while LH regains dominance in the chronic stage (Saur et al 2006)
Contribution of the right hemisphere to recovery

Negative effects:

- Some reports claim RH activation is associated with poor language performance
- Proposed mechanism I: reliance on ineffective RH regions prevents recovery of effective LH regions
- Proposed mechanism II: Negative feedback: left lesion releases from inhibition right homologues, which in turn may inhibit left regions even more.
Hierarchical model of aphasia recovery
(Heiss and Thiel 2006)

- Small left lesions or that do not touch critical language regions – complete recovery is possible by restoring normal LH activation
- Left lesions that affect critical language regions – perilesional LH cortex can help leading to good recovery
- Severe damage to left hemisphere networks – RH homologs recruited. Recovery will be partial because
  - RH regions not adept for that purpose
  - RH regions inhibit LH via transcallosal inhibition so LH can’t contribute even if its spared
1997). TMS and tDCS are safe noninvasive methods that can be used to induce or enhance neuroplastic changes in brain activity (Antal, Nitsche, & Paulus, 2001): a small but growing body of evidence indicates that noninvasive brain stimulation can have beneficial effects in the treatment of aphasia after stroke. These studies also inform our understanding of potential mechanisms of language recovery following injury to language networks.
TRANSCRANIAL MAGNETIC STIMULATION (TMS)

• TMS - a noninvasive method of depolarization of the neurons of the brain. TMS uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field.

• rTMS (repetitive transcranial magnetic stimulation)

• Used for treatment of various neurological and psychiatric disorders including migraines, strokes, Parkinson’s disease, depression and auditory hallucinations.
Transcranial Magnetic Stimulation (TMS)

- rTMS at low frequency (0.5-2Hz) decreases cortical activity
- rTMS at high frequency (>5Hz) increases cortical excitability

Naeser et al., 2005

Fig. 2. Illustration showing the TMS equipment and treatment procedure. An infrared camera is used to detect the position of the TMS coil. The 3D MPRAGE MRI scan of the participant is shown on a laptop computer used to guide positioning of the TMS coil directly over the targeted cortical region of interest (Brainsight, Rogue Industries, Montreal, Que.). The figure 8-shaped TMS coil is placed on the participant's scalp to affect brain cortex (approximately 1 cm × 1 cm) directly beneath the center of the coil.
Transcranial direct current stimulation (tDCS)

- Constant current (1-2mA).
- Current flows from Anode through brain to cathode
- Does not induce action potentials but changes resting potential of the membrane
- Different effect for anodal and cathodal stimulation:
  - Cathodal: decreased excitability
  - Anodal: increased excitability

Slide courtesy of Chris Rorden
tDCS vs TMS

- **Transcranial magnetic stimulation**
  - Relatively expensive (~$50,000).
  - Moderate sized effects (e.g. mild speech arrest).
  - Safe, but there are reports of inducing seizures when high amplitude and frequency are combined.
  - Causes resting neurons to **fire**.
    - Very brief pulse stops interrupts processing for ~30ms, can be used repetitively.
    - Depending on **frequency**, sustained TMS can induce excitability reduction (long-term depression) or enhancements (long-term potentiation) that can persist for hours or days.
tDCS vs TMS

- Transcranial direct current stimulation
  - Very inexpensive (~$250 for iontophoresis unit).
  - Believed to be exceptionally safe.
  - Does not cause resting neurons to fire (Purpura and McMurtry, 1965; Terzuolo and Bullock, 1956).
  - Believed to modulate the firing rate of active neurons.
    - Depending on polarity, tDCS can induce cortical excitability reduction or enhancement that persists for hours.

*Slide courtesy of Chris Rorden*
Effects persist

- Effects of tDCS persist after stimulation ends.
- Longer stimulation, slower return to baseline.

Nitsche et al. (2003)
Typical design

- Convention is to conduct behavioral task during and/or immediately after stimulation.
- E.G. Dockery reports that prefrontal tDCS polarity influences learning of Tower of London task – with effects seen 6-12 months later.
Using Transcranial Direct-Current Stimulation to Treat Stroke Patients With Aphasia

Julie M. Baker, PhD; Chris Rorden, PhD; Julius Fridriksson, PhD

Background and Purpose—Recent research suggests that increased left hemisphere cortical activity, primarily of the left frontal cortex, is associated with improved naming performance in stroke patients with aphasia. Our aim was to determine whether anodal transcranial direct-current stimulation (tDCS), a method thought to increase cortical excitability, would improve naming accuracy in stroke patients with aphasia when applied to the scalp overlying the left frontal cortex.

Methods—Ten patients with chronic stroke-induced aphasia received 5 days of anodal tDCS (1 mA for 20 minutes) and 5 days of sham tDCS (for 20 minutes, order randomized) while performing a computerized anoma treatment. tDCS positioning was guided by a priori functional magnetic resonance imaging results for each individual during an overt naming task to ensure that the active electrode was placed over structurally intact cortex.

Results—Results revealed significantly improved naming accuracy of treated items (F[1,9]=5.72, P<0.040) after anodal tDCS compared with sham tDCS. Patients who demonstrated the most improvement were those with perilesional areas closest to the stimulation site. Crucially, this treatment effect persisted at least 1 week after treatment.

Conclusions—Our findings suggest that anodal tDCS over the left frontal cortex can lead to enhanced naming accuracy in stroke patients with aphasia and, if proved to be effective in larger studies, may provide a supplementary treatment approach for anoma. (Stroke. 2010;41:1229-1236.)

Key Words: anoma ■ brain stimulation ■ functional magnetic resonance imaging ■ neuronal plasticity ■ recovery of function
tDCS treatment setup

- tDCS applied to left frontal region that showed max activation in an fMRI naming task

Figure. Example of the treatment setup. Patients trained on a computerized picture-word matching task (a) while receiving tDCS. During both A-tDCS and S-tDCS treatments, the anode electrode (b) was placed over the predesignated area on the scalp overlying the left frontal cortex while the reference cathode electrode (c) was placed over the right shoulder. The constant-current stimulator (d) was placed out of the patients’ sight behind a partition.

Baker et al., 2010
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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Immediate Posttreatment &gt; Baseline</th>
<th>1 Week Posttreatment &gt; Baseline</th>
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<tbody>
<tr>
<td></td>
<td>A-tDCS Treated Items</td>
<td>S-tDCS Treated Items</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
<td>Total</td>
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Scientific concerns

● Current is very small (1-2mA)
  – So tiny, many doubt neural effects are real.

● Behavioral effects typically very small
  – ‘File drawer problem’ most null results not counted.
  – Electrode placement crucial.
  – Controlling for experimenter demand crucial.
Where to stimulate

- Null result if stimulated region not involved with task.
- Visor neuronavigation system allows you to identify regions based on fMRI or MRI data.

Slide courtesy of Chris Rorden
Theoretical safety concerns

- Potential side effects with tDCS
  - Electrode-tissue interface could lead to skin irritation and damage.
  - Stimulations could lead to excitotoxic firing rates.
  - Tissue damage due to heating.
- Rat studies suggest injury only when current density is several orders of magnitude beyond those used in humans (Liebetanz et al. 2009).
- Standard doses in humans does not appear to alter serum neuron specific enolase (NSE), a sensitive marker of neuronal damage (Nitsche et al, 2003).
- Datta (2009) heating in humans is negligible.
Limitations

- Limited spatial resolution
  - Particularly tDCS (5x5cm electrodes)
  - Resolution is better with TMS but MRI guided coil placement is critical for accurate targeting of specific structures (e.g., pars triangularis)
  - Still lots of work on the mechanism of action
    - E.g., contrasting tDCS effects by Monti et al. 2008 vs. Baker et al., 2010
Stimulation effects in aphasia - summary

- Commonly used to inhibit right frontal regions, which may release left regions from inhibition
- tDCS also used to facilitate left frontal regions