Recent Advances in our Understanding of Neuroplasticity of Language Recovery

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Outline
- Epochs of recovery
- Neurophysiological changes underlying recovery
- Anatomical and physiological substrates of recovery
- Patterns of reorganization of language
  - Acute Stage
  - Sub-acute stage
  - Chronic stage
- Language recovery after rehabilitation
- A network approach to language rehabilitation

Epochs of recovery (Cramer, 2008)
- Acute injury
  - initial hours after a stroke
  - numerous profound changes evolve in blood flow, edema, metabolism, inflammatory state, and diaschisis
- Repair
  - first days after stroke onset, and lasts several weeks
  - most spontaneous behavioral recovery
  - endogenous repair-related events (BDNF, synaptogenesis, neuronal sprouting)
  - reach peak levels
- Chronic
  - weeks to months after stroke
  - spontaneous behavioral gains have generally reached a plateau
  - stable but still modifiable

Neurophysiological changes
Edema
- Reduction in cerebral blood flow
- Abnormal concentration /release of neurotransmitters
- Denervation
- Transneuronal degeneration
- Diaschisis

Neurophysiological changes in early recovery
Neurophysiological changes occur in the brain for a period of time following cerebral insult
- Edema
  - Like any other wound, brain damage causes edema
  - Occurs 2-3 days post onset
  - affects remote parts of the brain
  - shift of midline structures
  - behavioral deficits may be diffuse
  - diminishes about 1 week post onset
  - dead tissue removed by macrophages
  - distortions disappear
  - lesion becomes circumscribed
**Neurophysiological changes in early recovery**

Reduction in cerebral blood flow (hypoperfusion)
- Widespread ↓ function related to ↓ blood flow/metabolism of oxygen and glucose
- may last several months/longer

Abnormal concentration/release of neurotransmitters
- occurs immediately after infarction
- Due to ↑ activation/inhibition after damage to other parts of network
- Neurons release glutamate onto nearby neurons which become excited, overloaded with calcium and die

Denervation
- Decreased nerve supply
- Cells become really hypersensitive to neurotransmitters

Transneuronal degeneration
- Neurons or nerve cells may atrophy when they don’t have normal inputs

Cell A—Cell B
- Over time B dies without input from A

**Excitotoxicity**

Diaschisis (Von Monakow, 1914)
- "shocked throughout"
- ↓ responsiveness and dysfunction of intact neurons remote from damaged area
- May be related to ↓ in blood flow/metabolism and or abnormal neurotransmitter release
- Damaged area no longer sends signals to intact area

Flint et al., 2005

**Summary: Neurophysiological changes**

Edema
Reduction in cerebral blood flow
Abnormal concentration/release of neurotransmitters
Denervation
Transneuronal degeneration
Diaschisis

**Repair**

Neuronal regeneration
- Axons and dendrites can regenerate if cell body has remained

Synaptogenesis
- Formation of new synapses
- Cells that fire together wire together

Promoting repair
- BDNF
- Stimulation
In order for recovery of function to be restored to the infarcted hemisphere, its structural, functional and physiological integrity will need to be at optimal operability to sustain such recovery.

What are the patterns of reorganization of language?
- **Acute phase - reperfusion of tissue**
- **Sub-acute phase - resolution of diaschisis**
- **Chronic phase - the role of the ipsilesional hemisphere**

Sub-acute phase – resolution of diaschisis

Reperfusion can only salvage the ischemic penumbra for the first few days following ischemia and eventually, the hypo-perfused area often progresses to infarction (Chen & Yi-Cheng, 2012; Guadagno et al., 2008; Hillis et al., 2004).

Nonetheless, language recovery continues to occur in the ensuing months following the stroke.

Restoration of language function to the left hemisphere over time that corresponded with improvements in language function.
**Chronic phase- the role of the ipsilesional hemisphere**

Recovery of language either involves transferring language functions to the right hemisphere - (Weiller et al., 1995; Abo et al., 2004; Xu et al., 2004),

Or the exclusive recruitment of left perilesional and other left hemisphere areas - (Heiss & Thiel, 2006; Hillis, 2002; Karbe, et al., 1998; Rosen, et al., 2000; Saur et al., 2006).

Or a combination of the two (Crinion & Leff, 2007; Price & Crinion, 2005; Thompson & den Ouden, 2008).

Many parts of the brain could take over language function, but normal language areas inhibit this functioning.

So when language areas are damaged, releases inhibition from other areas capable of taking over language function.

Adjacent areas assume function

RH participation in language after LH infarction

- After substantial recovery in LH infarction, RH infarction results in loss of gains (Basso et al., 1989).


Sebastian & Kiran (2011)- Two tasks

- Semantic word judgment (a)- perilesional left frontal activation
- Picture Naming (b)- perilesional LH activation, but also RH activation

Sebastian & Kiran, 2011; Aphasiology

The more the damage to LIFG, LMTG and AG/SMG, the higher PSC in bilateral SFG, MFG, and ACC: serve as an assistive network in the case of damage to traditional language regions.

PSC in IFG pars opercularis and pars triangularis, despite significant damage, were the only regions to correlate with behavioral accuracy.

Summary of fMRI studies

Restoration of undamaged language dedicated regions in the left hemisphere is the most likely to result in long-term positive outcomes.

A less efficient but secondary mechanism involves compensation by intrahemispheric neighboring regions in the left hemisphere.

Finally, if damage to the left hemisphere is substantial, then homotopic regions in the contralateral (right) hemisphere are engaged in language recovery.

(Heiss et al., 2006. Brain and Language)

With regards to treatment for word retrieval, imaging studies have shown

<table>
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<tr>
<th>Right Hemisphere activation after treatment</th>
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<td>Peck et al., 2004; Crosson et al., 2005; Meinzer et al., 2006; Rabinyeu et al., 2008.</td>
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PET scans were performed on a picture naming task and results revealed increased activation in the right insular and right frontal regions as a function of treatment in 10 patients with aphasia.

Raboyeau et al., 2008; Neurology

Two of the three patients exhibited a trend toward improved naming, whereas the third did not.

Fridriksson et al. (2007); Neuropsychologia

Post-treatment fMRI once again revealed bilateral changes in activity, located not just in language-related cortex but also in regions outside of the traditional language regions.

Fridriksson et al. (2007); Neuropsychologia

26 patients with aphasia who received consecutive semantic and phonological cueing therapy to improve naming.

Results revealed an increase in left hemisphere undamaged frontal and parietal regions in patients who demonstrated an improvement in naming skills after treatment.

Fridriksson (2010); JNeuroscience

Abel et al., 2015; Brain

With regards to treatment for word retrieval, imaging studies have shown

Peck et al., 2004; Crosson et al., 2005; Meinzer et al., 2006; Raboyeau et al., 2008.

White matter changes as a function of language recovery

Schlaug et al. 2009; ANVAS

Brier et al., 2011; Neurocase
With regards to treatment for word retrieval, imaging studies have shown:

- Right Hemisphere activation after treatment
- Bilateral activation after treatment
- Left hemisphere/perilesional activation after treatment

Peck et al., 2004; Crosson et al., 2005; Manner et al., 2006; Raboyeau et al., 2008;
Fridriksson et al., 2006; Fridriksson et al., 2007; Leger et al., 2002; Fridriksson et al., 2010

A few studies have examined changes in network connectivity after rehabilitation (Abutalebi et al., 2009; Vitali et al., 2010; Sarasso et al., 2010).

- Single case(s) studies
- Show effects of training can be reflected in modulations of connectivity

Network changes after rehabilitation

Specific patterns of activation may inform regions that may change—but not necessarily how they are modulated within a network.

Understanding changes in activation and changes in network connectivity will provide a better understanding of the dynamics of language recovery.

For both patients, more connections that were strengthened appeared during trained items than during untrained items.

Patient with the larger lesion had more connections strengthened in RH
Patient with the smaller lesion had more connections strengthened in LH

Vitali et al., 2010; Neurocase

Picture naming and semantic feature processing

Indefrey & Levelt, 2004, Cognition

Binder & Desai, 2011 (TICS)

Treatment and generalization based on complexity

Kiran & Thompson, 2003; Kiran, 2007; Kiran & Johnson, 2008; Kiran, 2008; Kiran et al., 2006; Kiran et al., 2011

Kiran et al., 2015, Frontiers in Human Neuroscience
fMRI of treatment-induced neuroplasticity

The region with the highest node degree in the trained abstract difference network is the left inferior frontal gyrus pars triangularis (L IFGtri).

The regions with the highest node degree in the generalized concrete difference network were L SupMed and R IFGtri.

The regions with the highest node degree in the non-generalized concrete difference network were L MFG and R IFGorb.

The size of each sphere represents the number of participants who show significant increases in connectivity for that region, while the color of the sphere represents the average node degree for the majority (at least 2/3) of participants.

Changes in BOLD signal from pre- to post-treatment for abstract and concrete words at the group level. Red spheres indicate peaks of activation for the one-sample t-test of the [post-treatment abstract > pre-treatment abstract] contrast for the group of responders (n = 9). Blue spheres indicate peaks of activation for the one-sample t-test of the [post-treatment concrete > pre-treatment concrete] contrast for the group of generalizers (n = 7).

A ‘Revised” Summary of fMRI studies

Restoration of undamaged language dedicated regions in the left hemisphere is the most likely to result in long-term positive outcomes.

A less efficient but secondary mechanism involves compensation by intrahemispheric neighboring regions in the left hemisphere.

Finally, if damage to the left hemisphere is substantial, then homotopic regions in the contralateral (right) hemisphere are engaged in language recovery.

Other regions: DOMAIN GENERAL REGIONS also participate in recovery.

Other regions: DOMA
Summary

Language recovery is enabled by a network of language regions that includes:

- Undamaged regions in the left hemisphere
- Prefrontal regions such as MFG and SFG serve a supportive role
  - Part of a multiple demand network where activation in domain-general regions influences activation in spared tissue in domain-specific regions (Fedorenko et al., 2012).
  - SFG and ACC serve a regulatory role to modulate function (Kiran et al., 2015)
- RH regions such as RIFG and RMFG play a crucial supportive role

Promoting reorganization

1. Use it or lose it

Kamins et al., 2012, JNerosciences
Repurposed cortex

Fridriksson et al. (2007); Neuropsychologia

2. Use it and improve it

Abel et al., 2015
Sandberg et al.; 2015, Brain and Language

3. Specificity, 4. Repetition

Abel et al., 2015; Neuropsychologia

3. Specificity
  - Changes in the brain specific to what is trained - not diffuse effects

4. Repetition matters
  - Single or few trials not sufficient to promote facilitative long term potentiation/learning

5. Intensity, 6. Time

5. Intensity matters
  - In chronic aphasia, Persad and colleagues reviewed outcomes from rehabilitation centers that provide intensive comprehensive aphasia treatment and reported positive outcomes: Persad et al. (2013). Topics in Stroke Rehabilitation.

6. Time matters
7. Salience, 8. Age, 9. Transference, 10. Interference

7. Salience matters
- Attention, motivation, meaning, reward, emotion

8. Age matters
- Neurogenic response is reduced with age
- Exercise increases neurotrophic factors

9. Transference
- Successful and unsuccessful generalization has different consequences in the brain (Sandberg et al., 2015)

10. Interference
- Maladaptive compensatory strategies (RH) (Rehme et al., Neuroimage 2011)

Summary

Achieve functional communication independence

Post stroke aphasia

Graph Theoretical Analysis

Semi-partial correlations regions in the difference (post-pre treatment matrix)

Node degree
- How many different regions is this node increasing its connections with?
- Sum of number of connections that are significantly increasing in correlation strength
  - Significance determined with 95% CI
  \[ k = \frac{1}{2} (n^2 - n) - \sum m \leq \frac{3\sqrt{n}}{2} \]
  - \( AG = 3; PCN = 2 \)

BCAconnectivity methods

Normal network


Pre Treatment

Post Treatment

Abakke et al., 2009; Kahn & Polynne, 2013; Seghier et al., 2010; Schofield et al., 2012