BOSTON UNIVERSITY

Recent advances in our understanding of Neuroplasticity of Language Recovery

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Disclosure

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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
- Promoting reorganization in the brain- What can the clinician do?

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

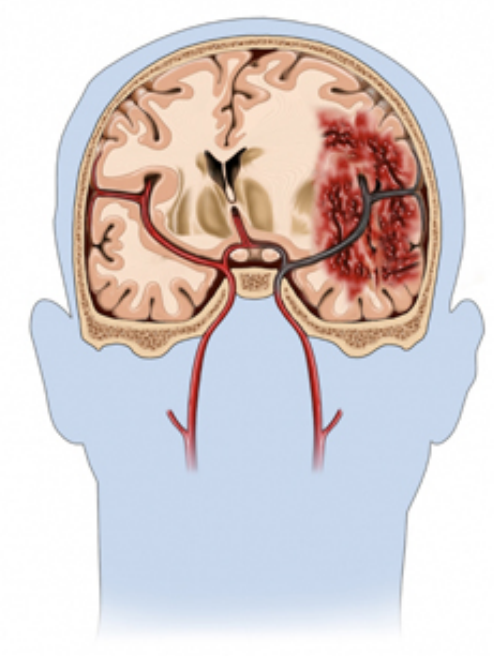
Diaschisis

Neurophysiological changes in early recovery

Neurophysiological changes occur in the brain for a period of time following cerebral insult

Edema

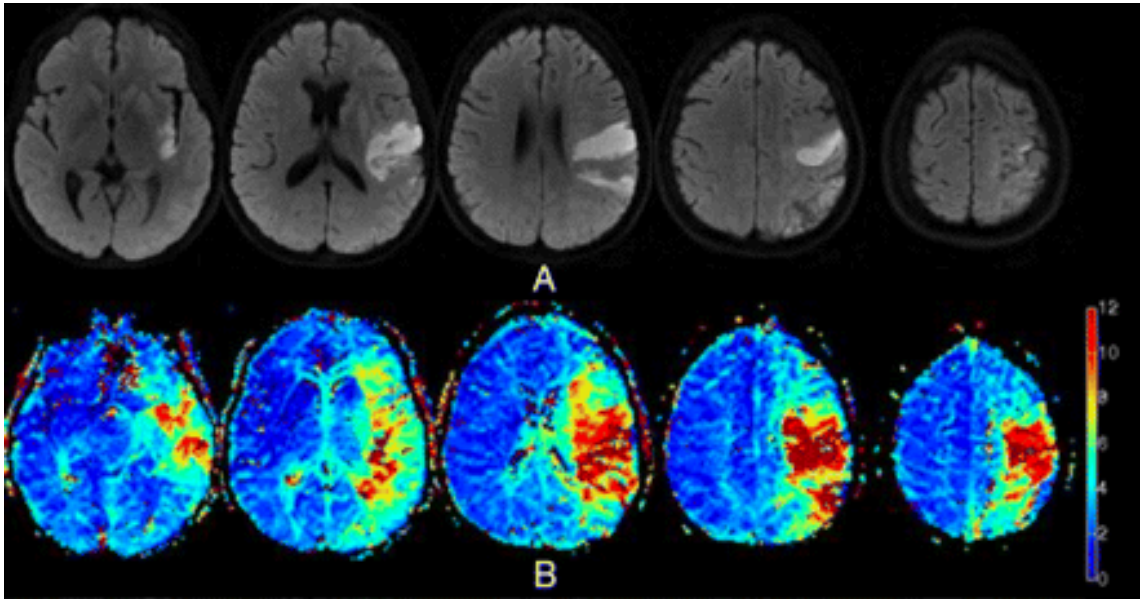
- Like any other wound, brain damage causes edema
- Occurs 2-3 days post onset
- affects remote parts of the brain
  - shift of midline structures
  - behavioral deficits may be diffuse
- diminishes about 1 week post onset
  - dead tissue removed by macrophages
  - distortions disappear
  - lesion becomes circumscribed



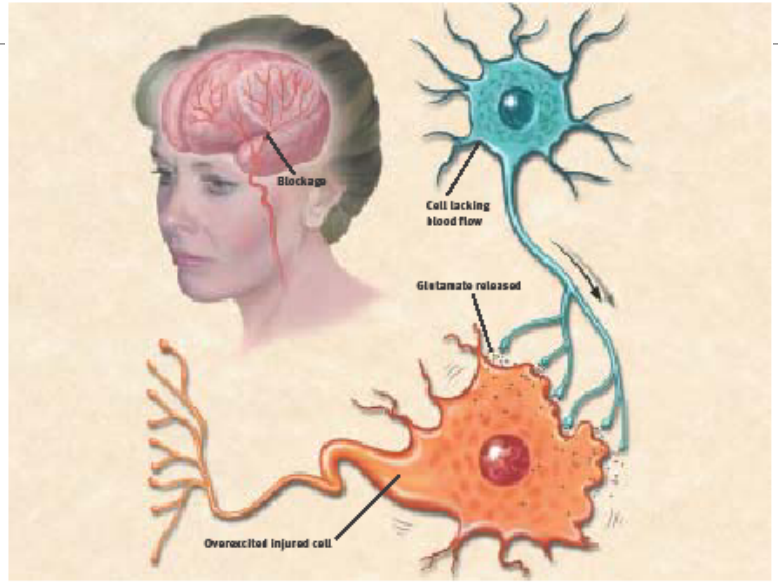
Neurophysiological changes in early recovery

Reduction in cerebral blood flow (hypoperfusion)

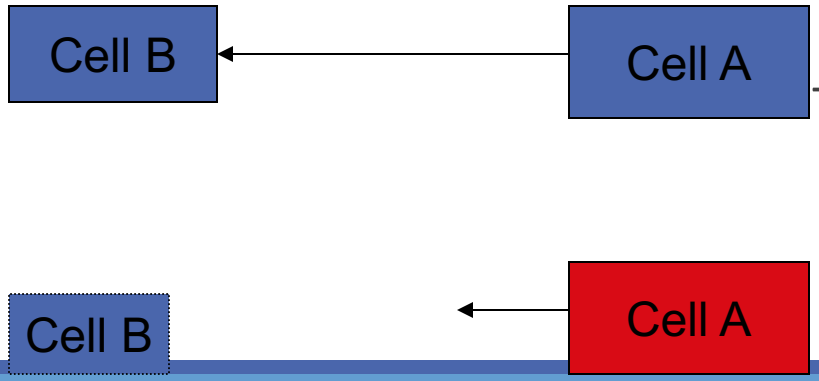
- Widespread ↓ function related to ↓ blood flow/metabolism of oxygen and glucose
- may last several months/longer



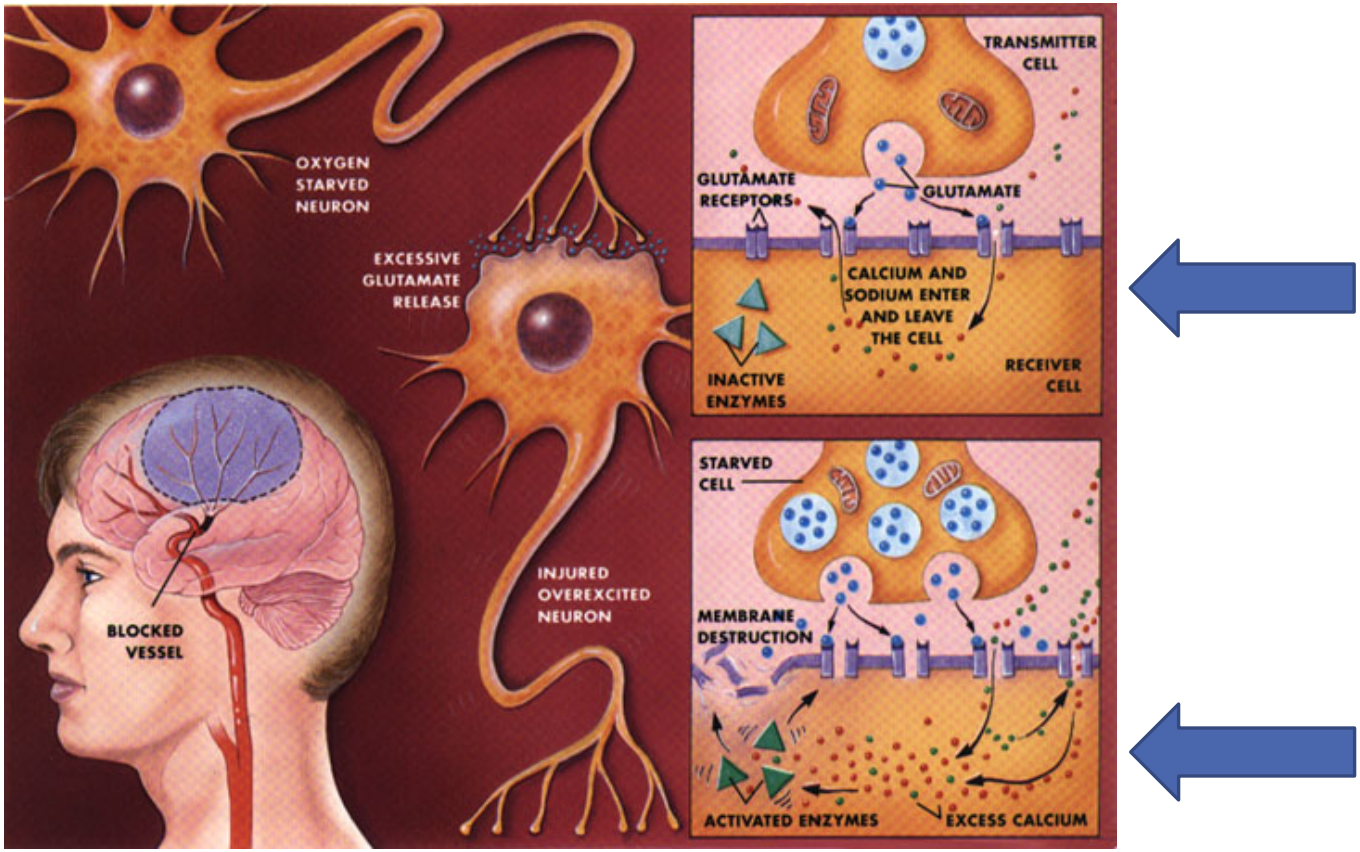
Neurophysiological changes in early recovery



- 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



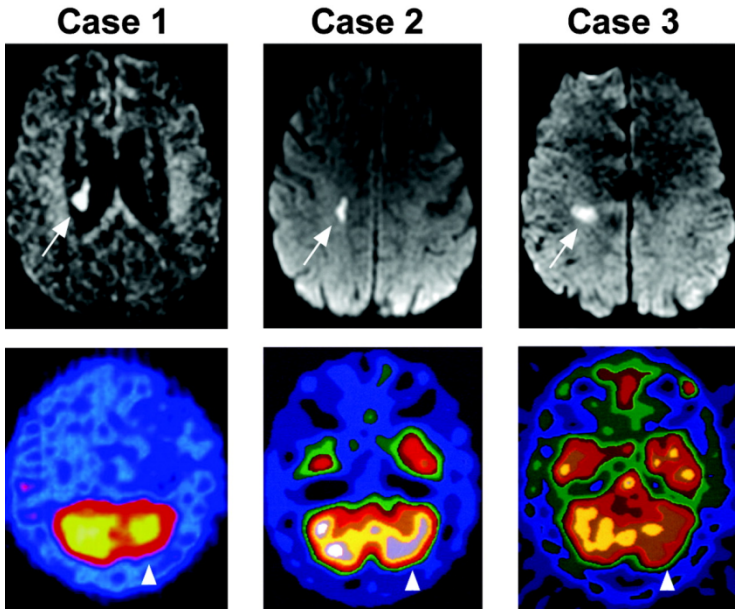
Excitotoxicity



Neurophysiological changes in early recovery

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

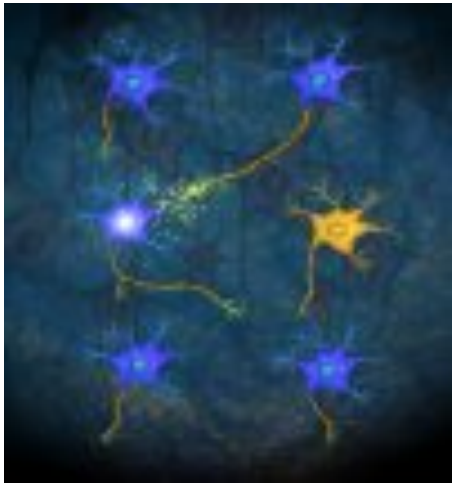
Diaschisis

Repair

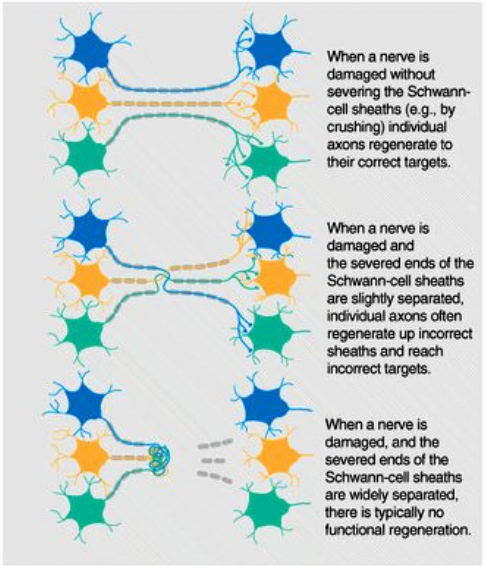
Neuronal regeneration
- Axons and dendrites can regenerate if cell body has remained

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

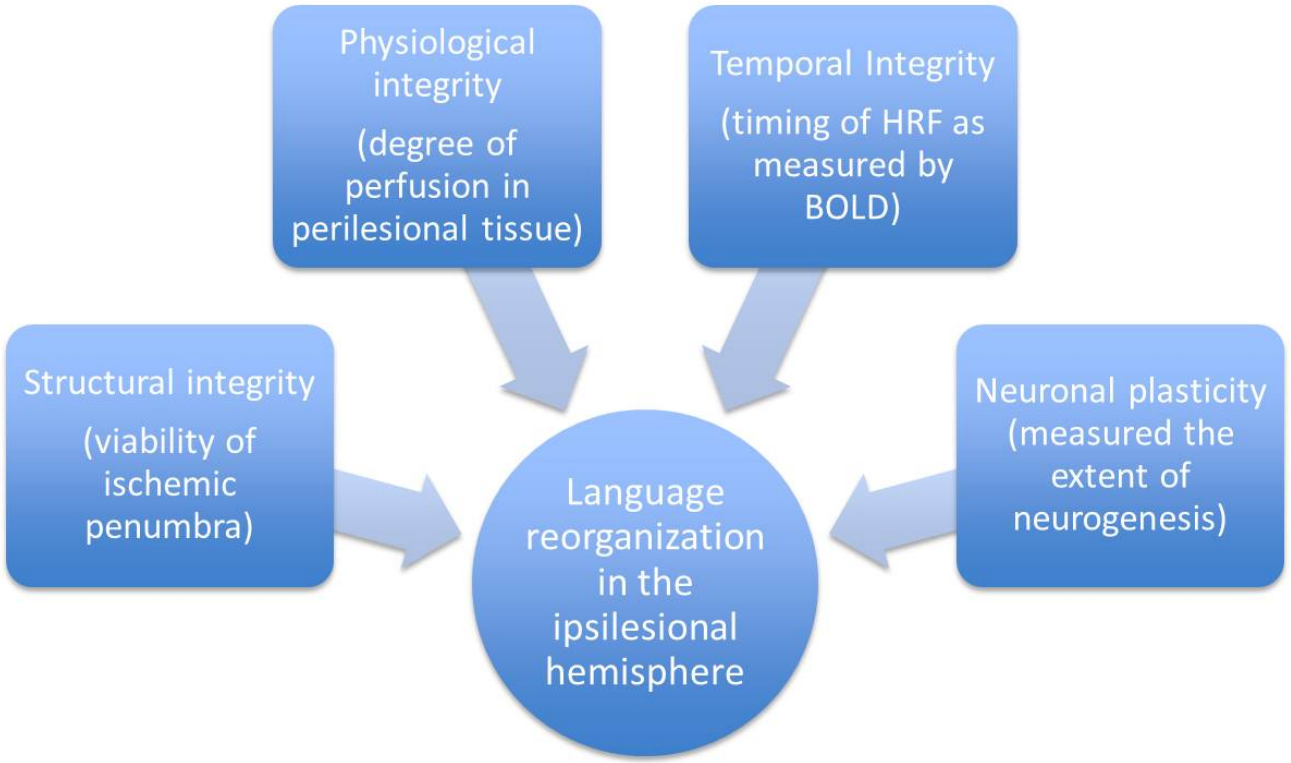
Promoting repair
- BDNF
- Stimulation



► Three Patterns of Axonal Regeneration



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 operationality to sustain such recovery

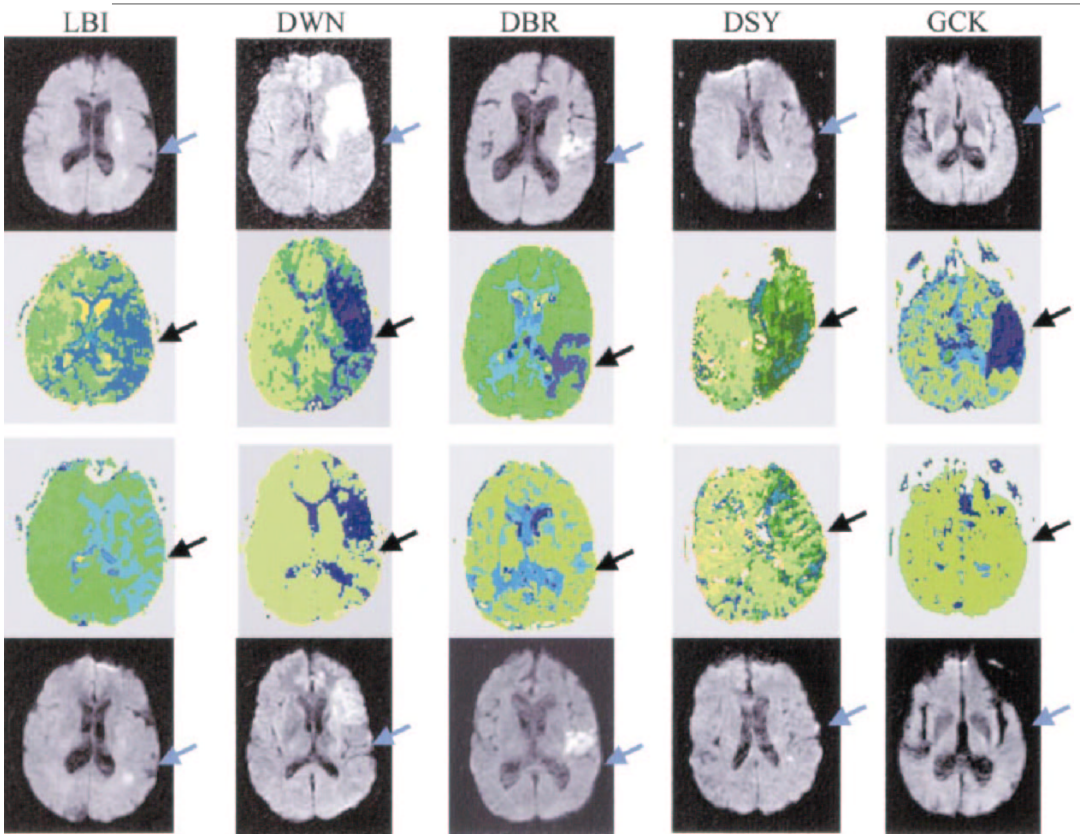


Kiran, 2012; ISRN

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*

Acute phase - reperfusion of tissue



Hillis et al., 2001

Language recovery in the acute phase (typically in the first few weeks after the infarct) is mostly determined **by the extent of successful reperfusion of the infarcted tissue** in order to restore language function.

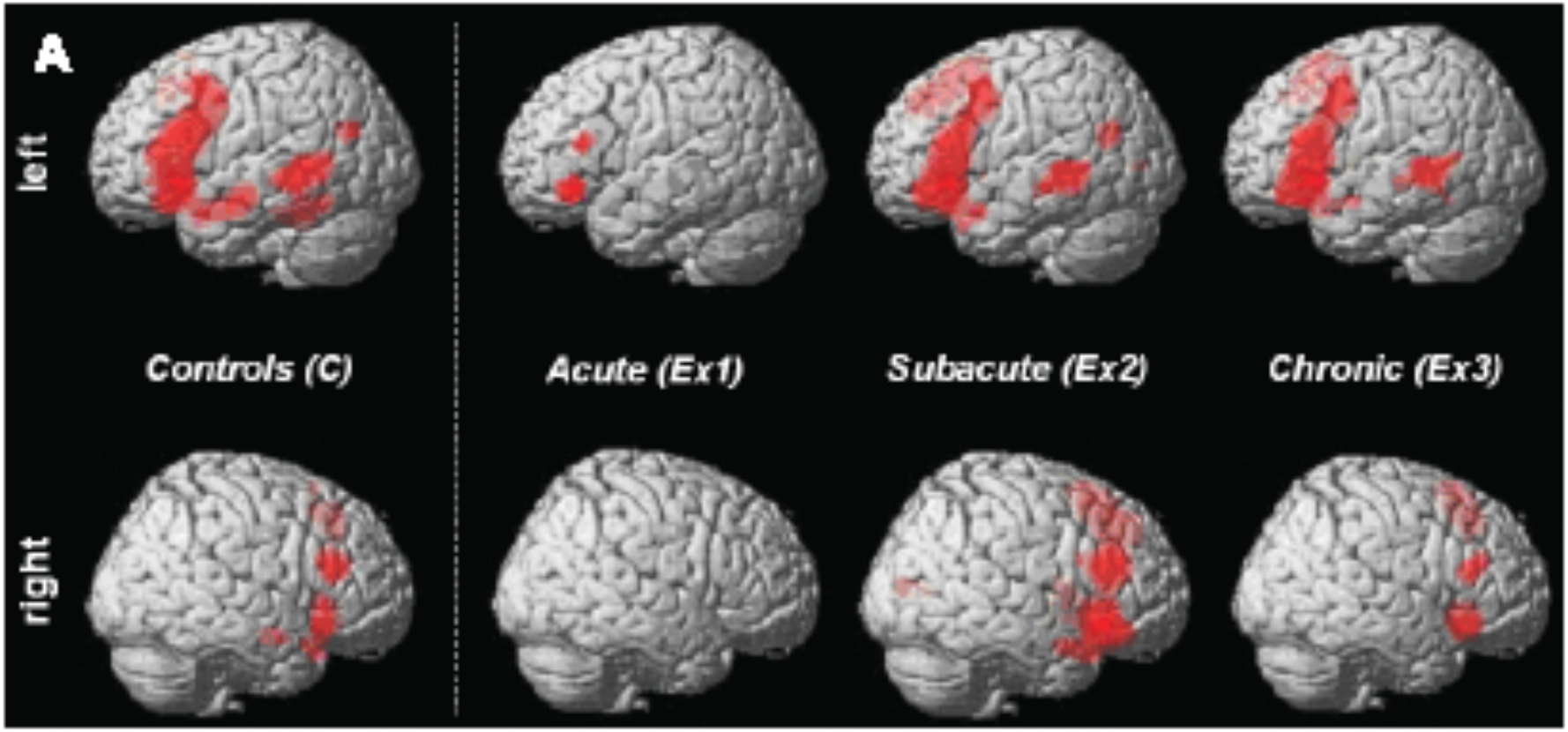
FIG. DWI and PWI scans before treatment (top two rows) and during treatment (lower two rows) for patients who showed improved lexical-semantics with treatment. Arrows point to BA 22.

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.

Sub-acute phase –resolution of diaschisis



Saur et al., 2006; Brain

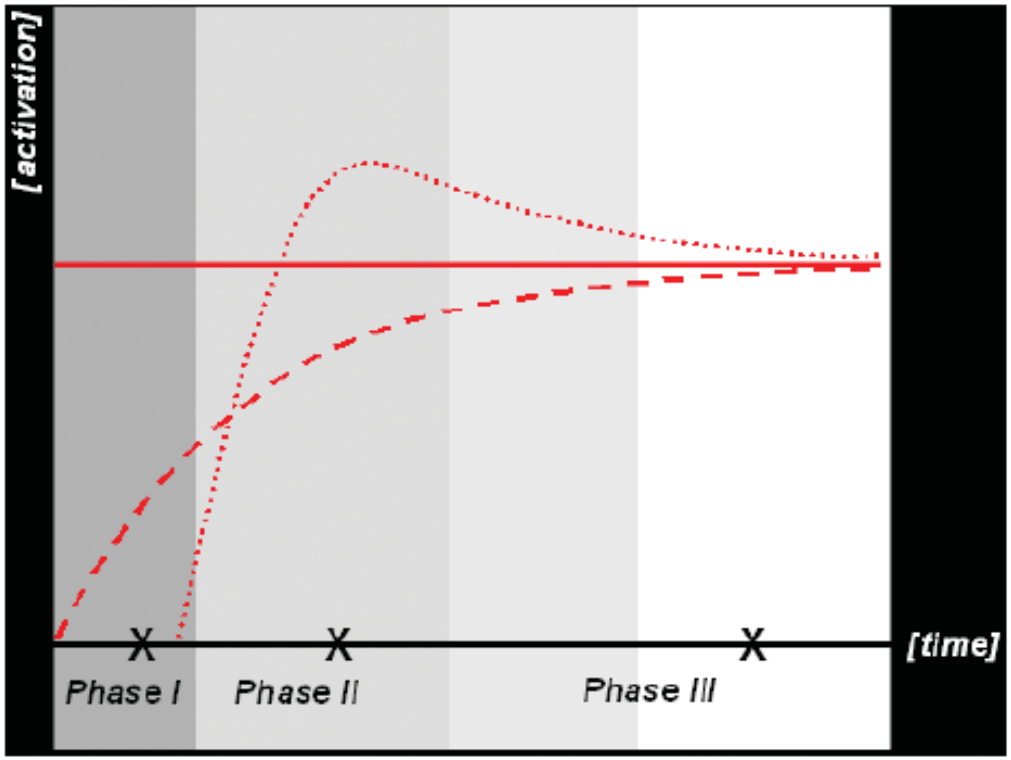


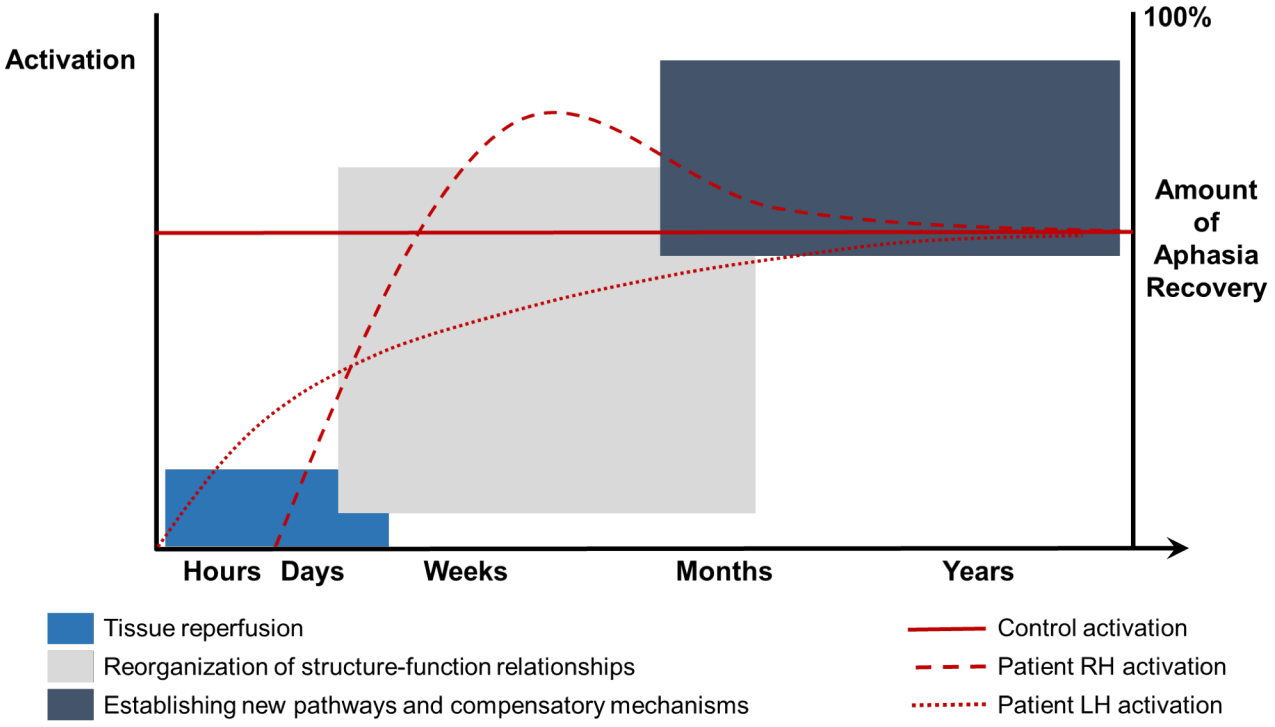
Fig. 5 Model with three phases of language recovery after stroke. Three phases of language recovery: Acute Phase I characterized by loss of function; Subacute Phase II by an upregulation of the language network; Chronic Phase III by a consolidation and normalization of activation. Diagrammed activation of controls (—), left language areas (---) and right language areas of aphasic patients (···). Crosses (X) indicate time of fMRI (examinations 1, 2 and 3).

Restoration of **language function to the left hemisphere** over time that corresponded with improvements in language function

Saur et al., 2006; Brain

Slide courtesy- Erin Meier

What constitutes neural recovery in aphasia?



Hillis & Heidler, 2002; Saur et al., 2006

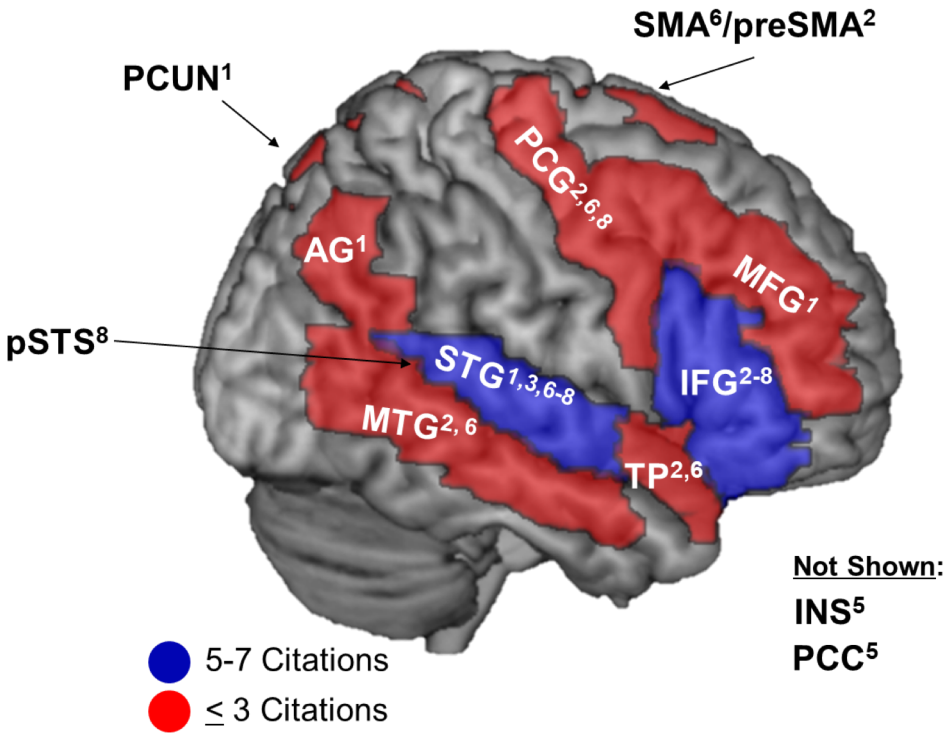
Neural correlates of language recovery in PWA

Slide courtesy- Jeff Johnson

- Evidence that the right hemisphere supports language recovery and/or is recruited via language treatment

[1]Gold & Kertesz, 2000 (NT)
[2]Crosson et al., 2005 (T)
[3]Meinzer et al., 2006 (T)
[4]Vitali et al., 2007 (T)
[5]Raboyeau et al., 2008 (T)
[6]Fridriksson et al., 2009 (NT)
[7]Mohr et al., 2014 (T)
[8]Skipper-Kallal et al., 2017 (NT)

T = Treatment Study
NT = Non-treatment Study



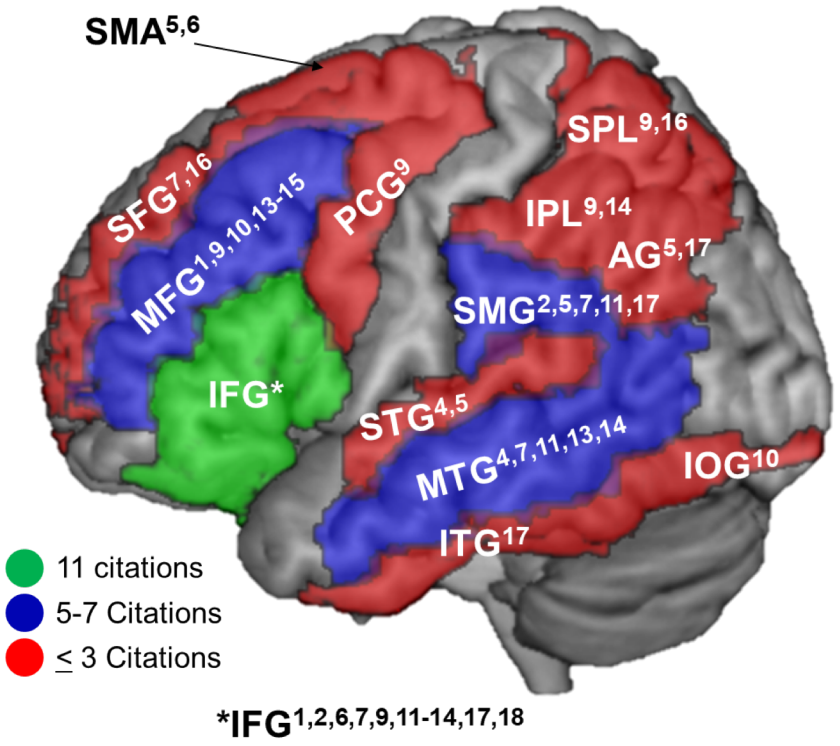
Neural correlates of language recovery in PWA

- Evidence that better recovery and treatment outcomes are achieved when activation returns to the left hemisphere

[1]Cao et al., 1999 (NT)
[2]Leger et al., 2002 (T)
[3]Perani et al., 2003 (NT)
[4]Fernandez et al., 2004 (NT)
[5]Crosson et al., 2005 (T)
[6]Saur et al., 2006 (NT)
[7]Vitali et al., 2007 (T)
[8]Meinzer et al., 2008 (T)
[9]Fridriksson, 2010 (T)
[10]Fridriksson et al., 2010 (NT)
[11]Rochon et al., 2010 (T)
[12]Van Oers et al., 2010 (NT)
[13]Sebastian & Kiran, 2011 (NT)
[14]Szaflarski et al., 2011 (NT)
[15]Allendorfer et al., 2012 (NT)
[16]Szaflarski et al., 2013 (NT)
[17]Van Hees et al., 2014 (T)
[18]Sims et al., 2016 (NT)

T = Treatment Study
NT = Non-treatment Study

Not shown:
medFG[10,15]
ACC[10,15]
PCUN[7,9]



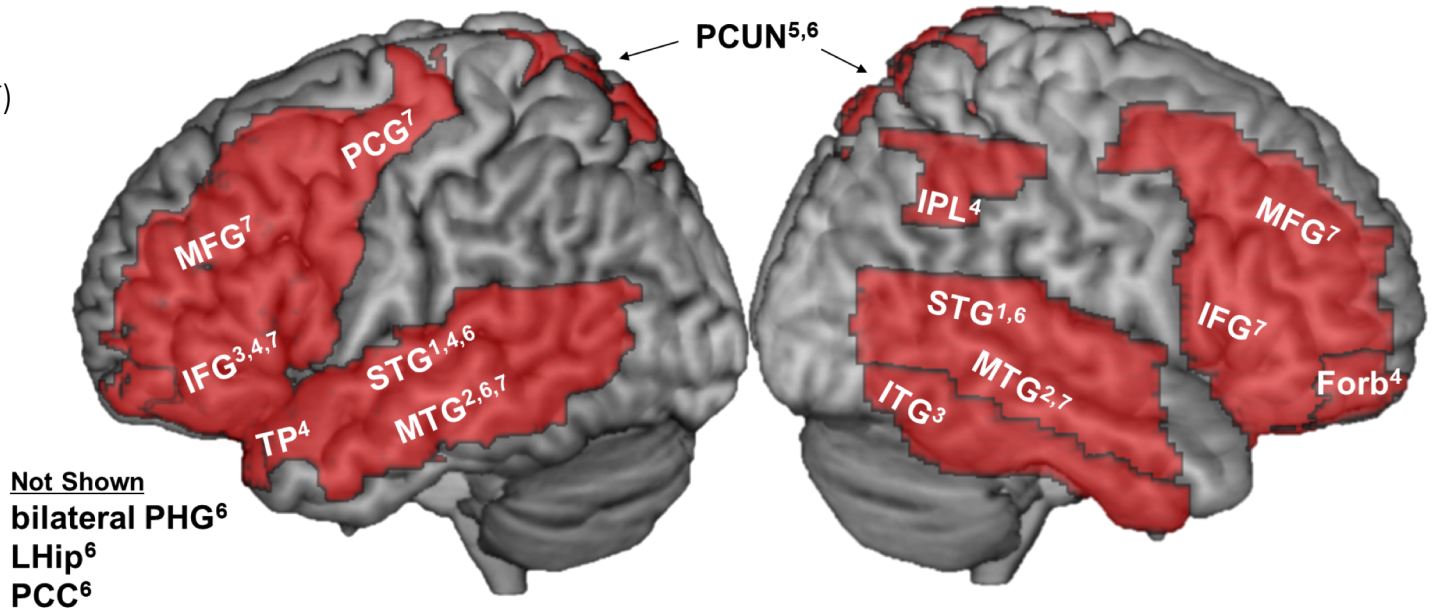
***IFG[1,2,6,7,9,11-14,17,18]**

Neural correlates of language functions in PWA

Slide courtesy- Jeff Johnson

- Studies linking behavioral recovery to increased activation in regions in both hemispheres

[1]Cardebat et al., 2003 (NT)
[2]De Boissezon et al., 2005 (NT)
[3]Davis et al., 2006 (T)
[4]Fridriksson et al., 2006 (T)
[5]Fridriksson et al., 2007 (T)
[6]Menke et al., 2009[6] (T)
[7]Kiran et al., 2015 (T)



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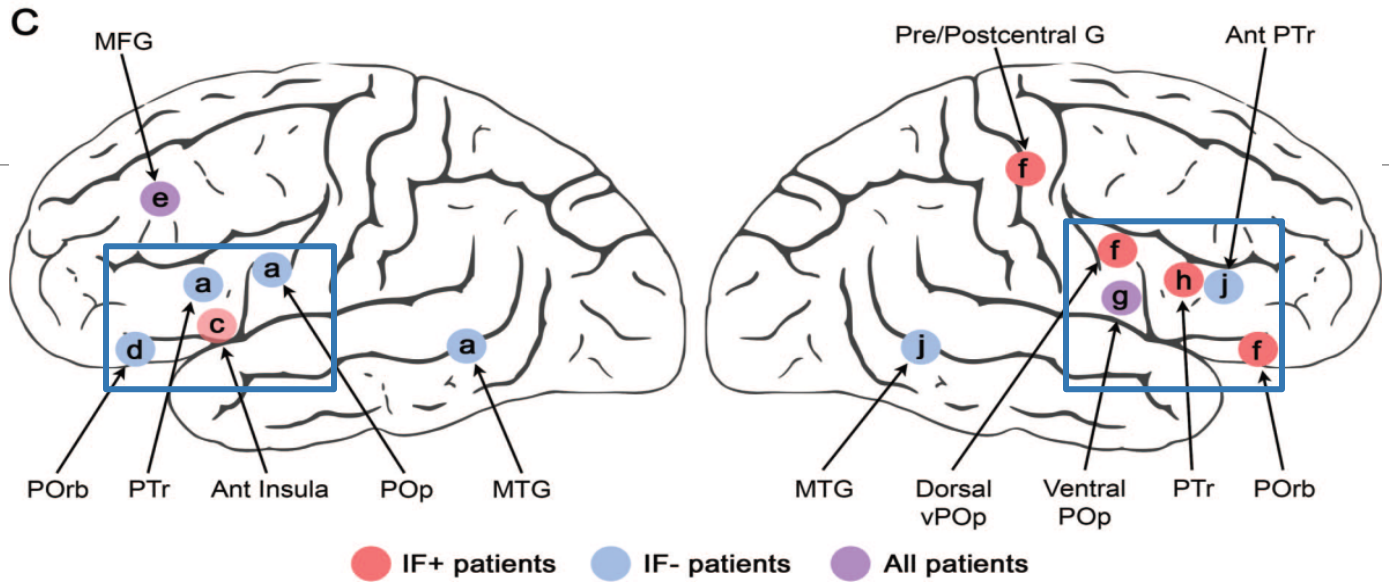


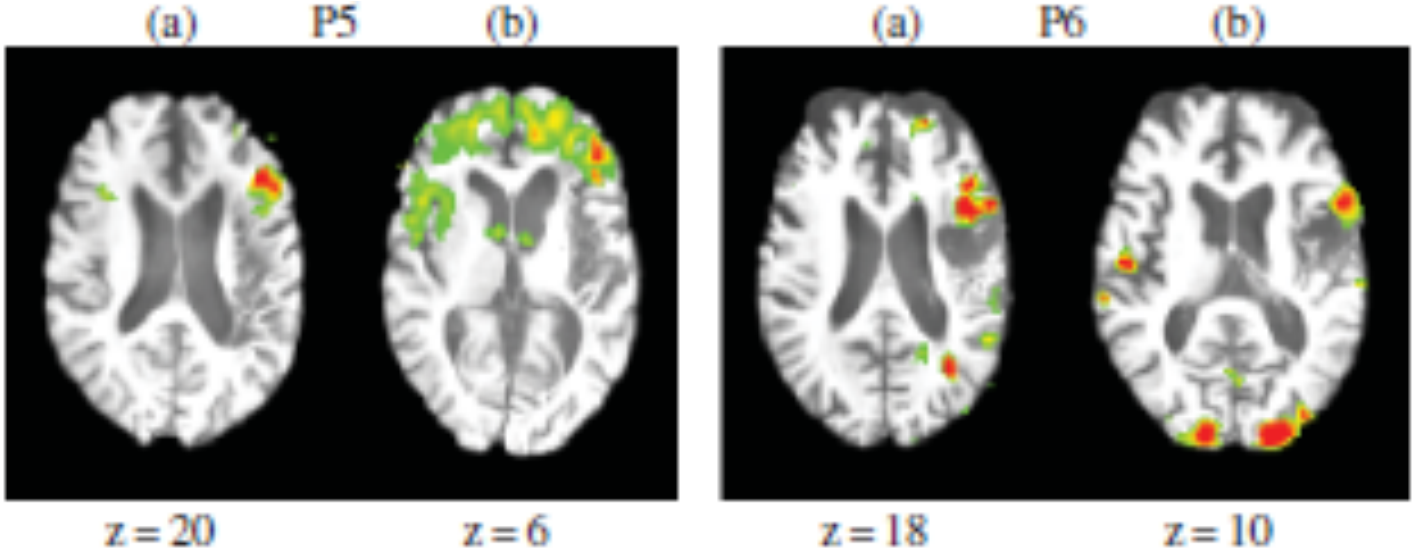
So when language areas are damaged, releases inhibition from other areas capable of taking over language function

Adjacent areas assume function

↑ RH participation in language after LH infarction

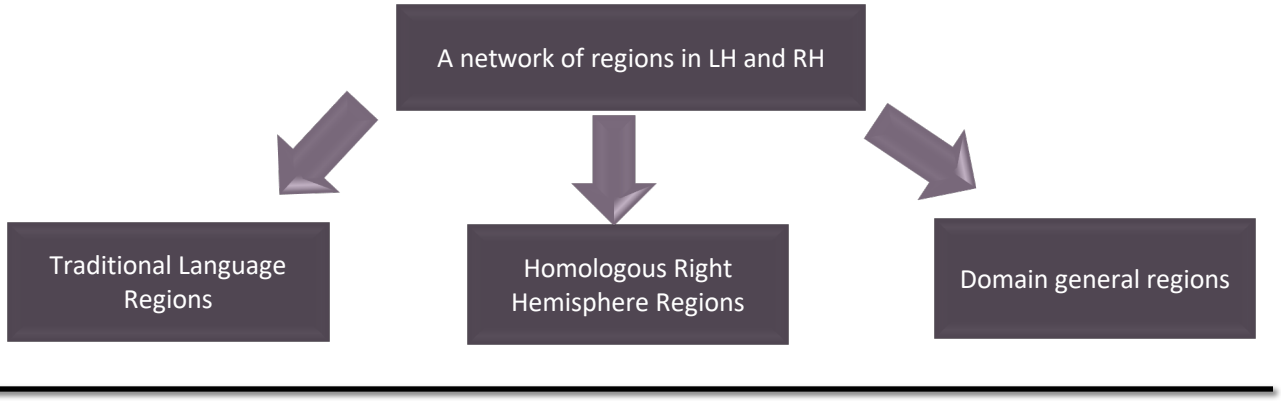
Turkeltaub et al., 2011, Neurology

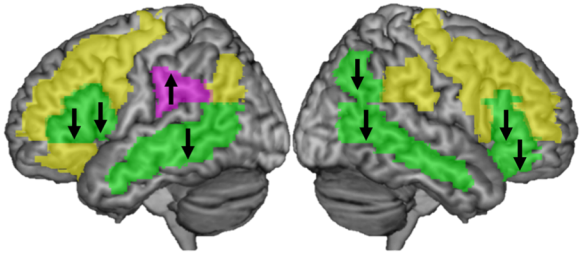
- Semantic word judgment (a)- perilesional left frontal activation
- Picture Naming (b)- perilesional LH activation, but also RH activation
- Depending on task demands, may see **LH or bilateral activation**

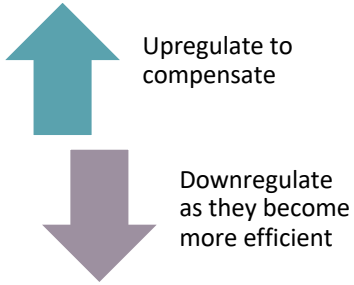


Sebastian & Kiran, 2011; Aphasiology

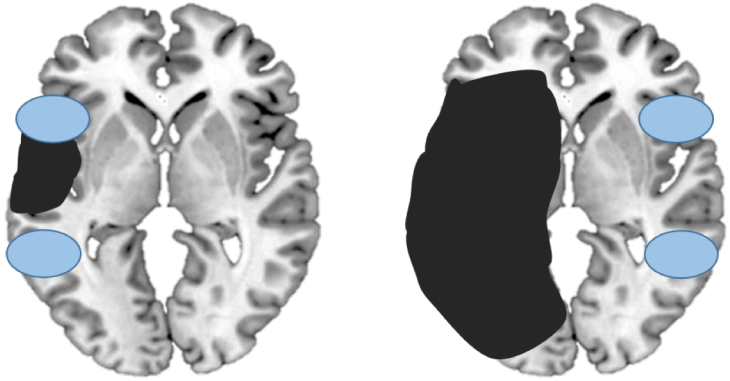
Understanding language recovery-where we are..



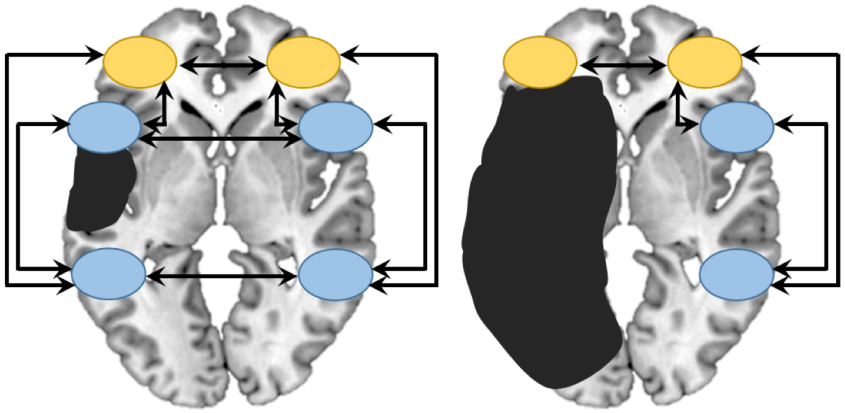




Traditional view of recovery

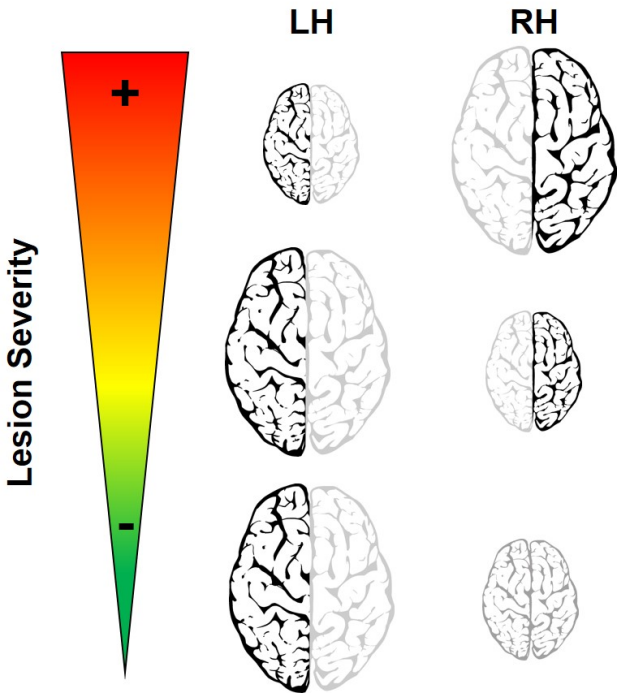


Network view to recovery



- Typical activity patterns & language abilities are *not* always restored by the chronic phase of recovery

- Model of recovery in chronic aphasia:
  1. **Optimal (possibly complete) behavioral recovery:** minor damage to left hemisphere (LH) regions not central to language
  2. **Satisfactory (but incomplete) behavioral recovery:** damage to core LH language regions but LH perilesional tissue remains functional
  3. **Poor behavioral recovery:** extensive damage to entire LH; only homotopic RH regions remain for language

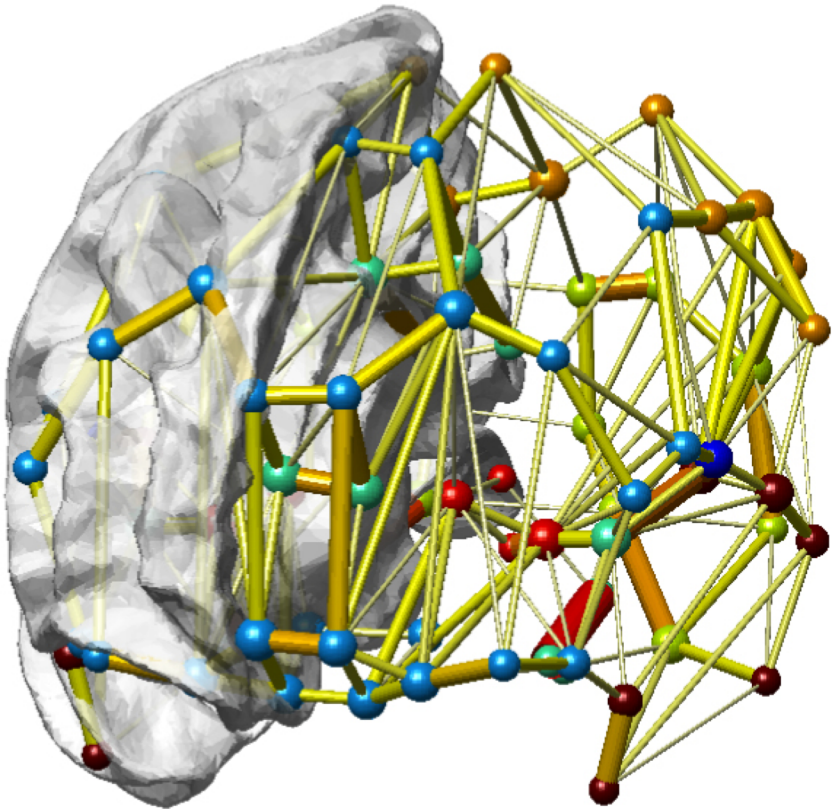


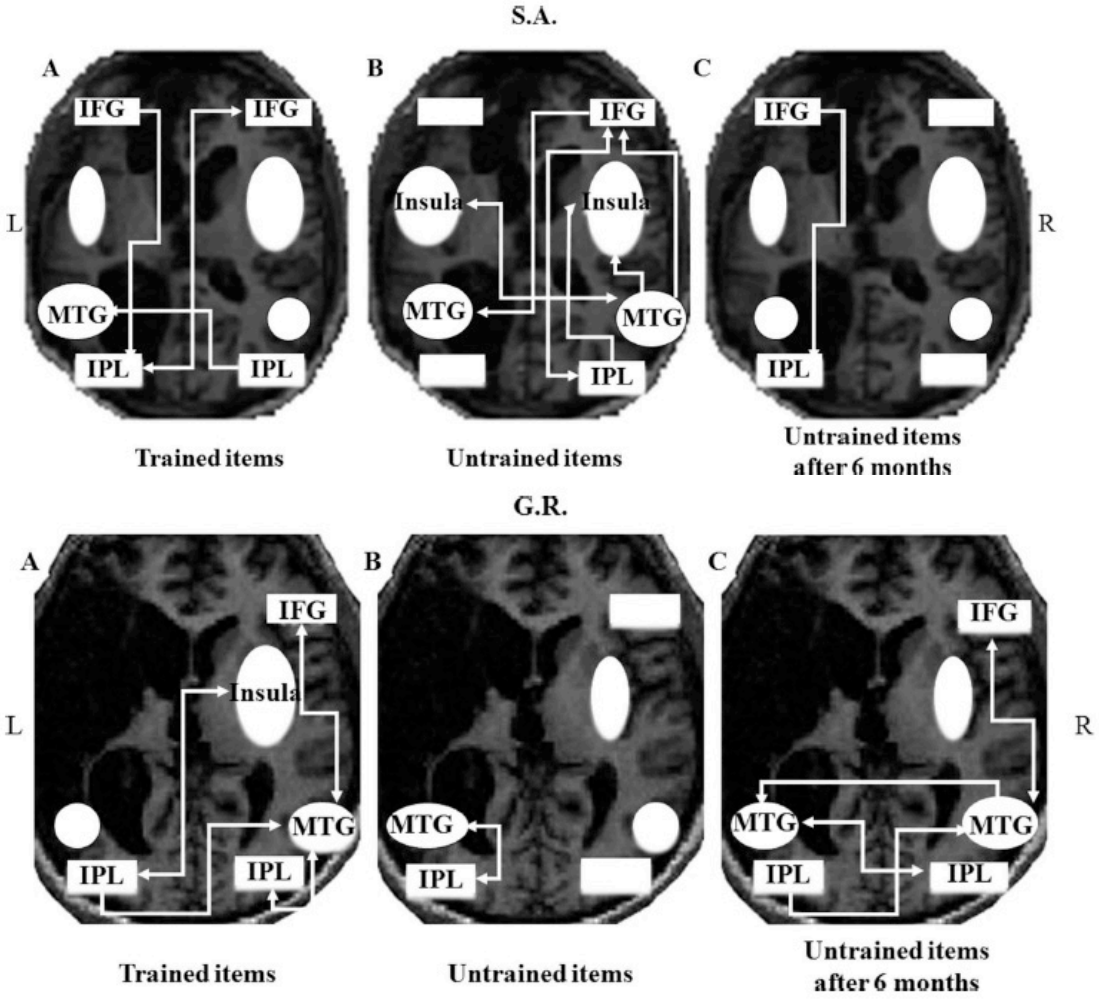
Heiss & Thiel, 2006; Anglade, Thiel, & Ansaldo, 2014

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.



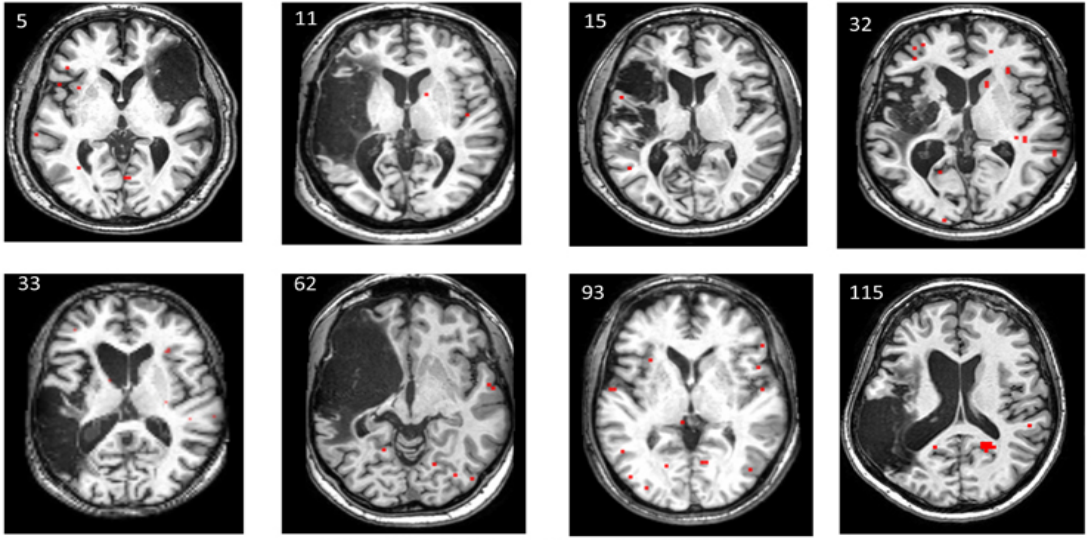


For both patients, **more connections that were strengthened** appeared during **trained items than during untrained items**.

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



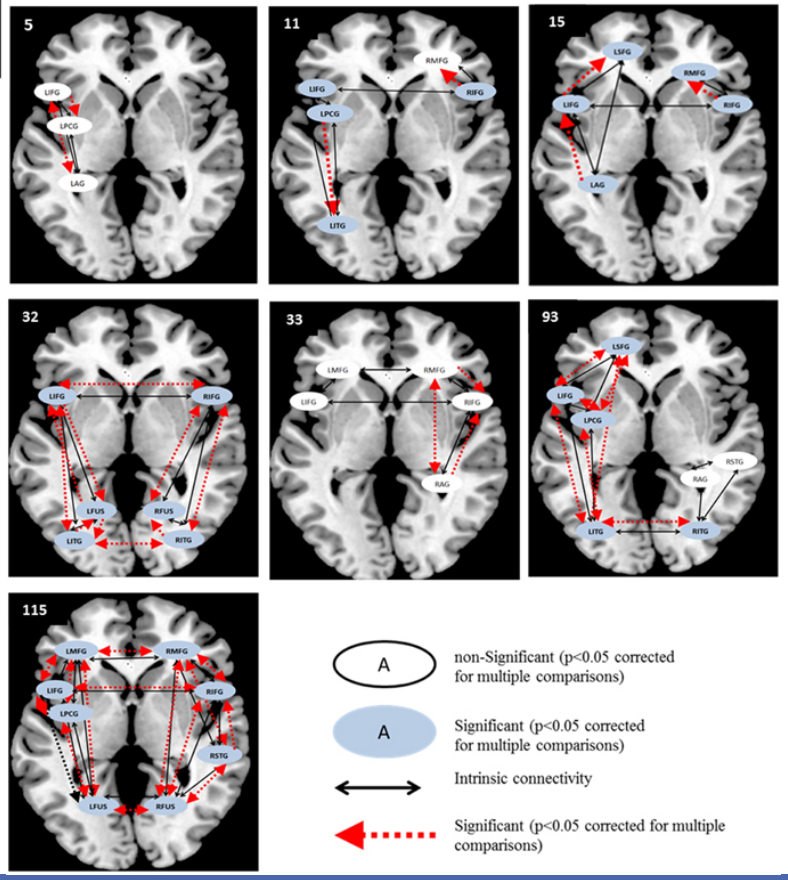
PICTURE NAMING: activations for individual patients
Uncorrected p=0.001 (T>3.1)

LIFG was the most consistently active VOI in the pre- and post-rehabilitation scans and the most consistently **significantly modulated region** as a function of rehabilitation

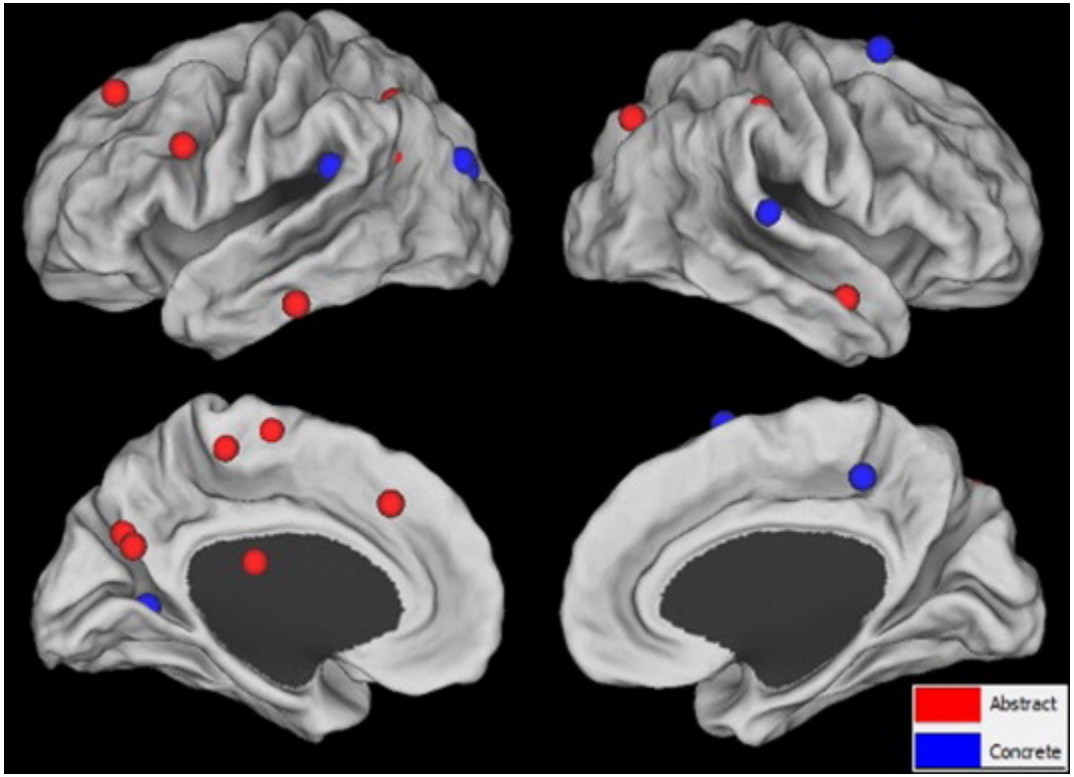
Next, **LPCG** and **RIFG** also consistently modulated regions

RIFG-RMFG and **LIFG-LPCG** most consistently modulated connections

DCM modulations for individual patients



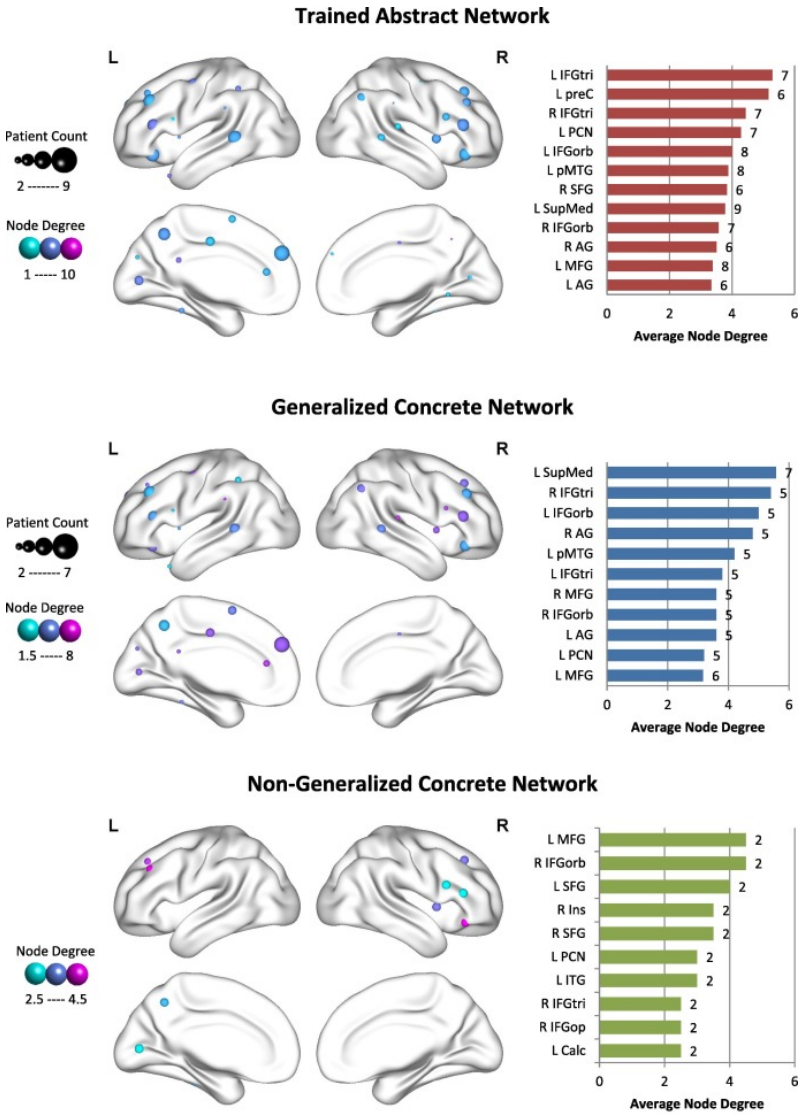
Kiran et al; 2015, Frontiers in Human Neuroscience



Changes in BOLD signal from pre- to post-treatment for abstract and concrete words at the group level.

LH regions show changes in activation for abstract items as a function of abstract treatment. Different regions show changes for concrete items.

Sandberg et al; 2015, Brain and Language



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. Higher values are more purple, lower values are more turquoise. The bar graphs highlight the regions with the highest node degree for the majority (at least 2/3) of participants.

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

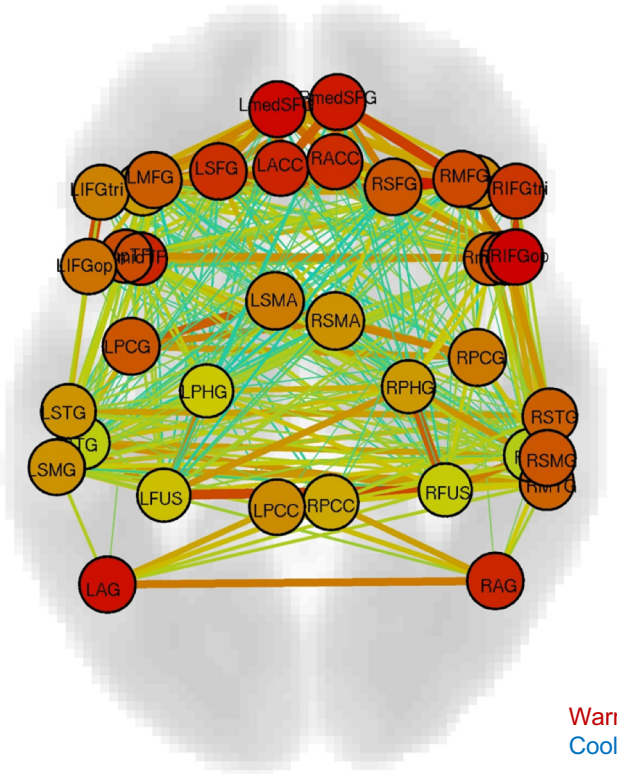
The regions with the **highest node degree** in the generalized concrete difference network were **L SupMed and R IFGtri.**

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

Sandberg et al; 2015, Brain and Language

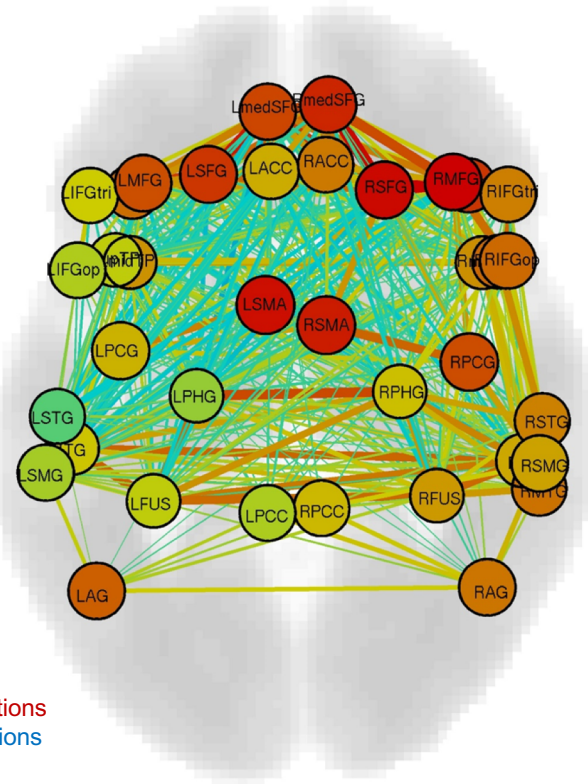
Controls

-27.05 27.05



PWA

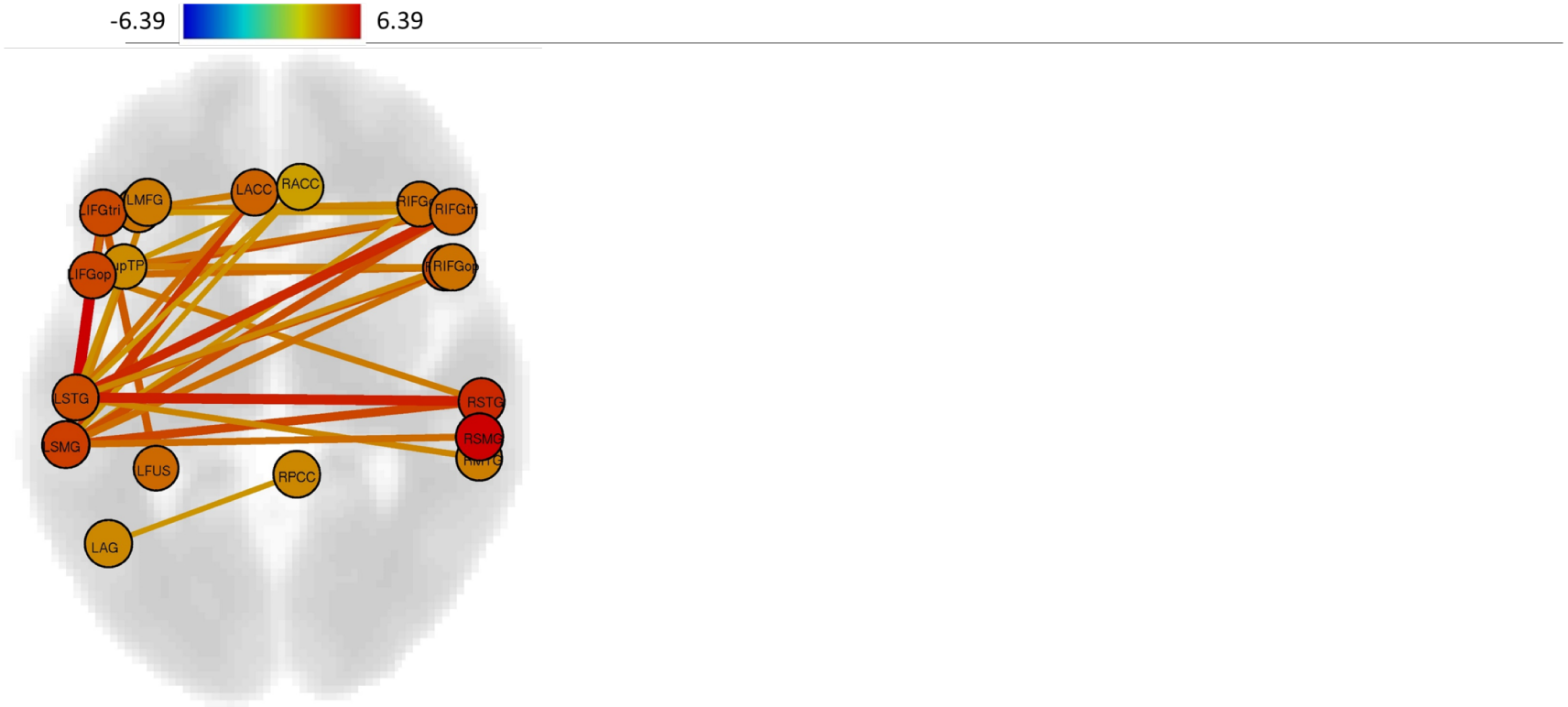
-27.08 27.08



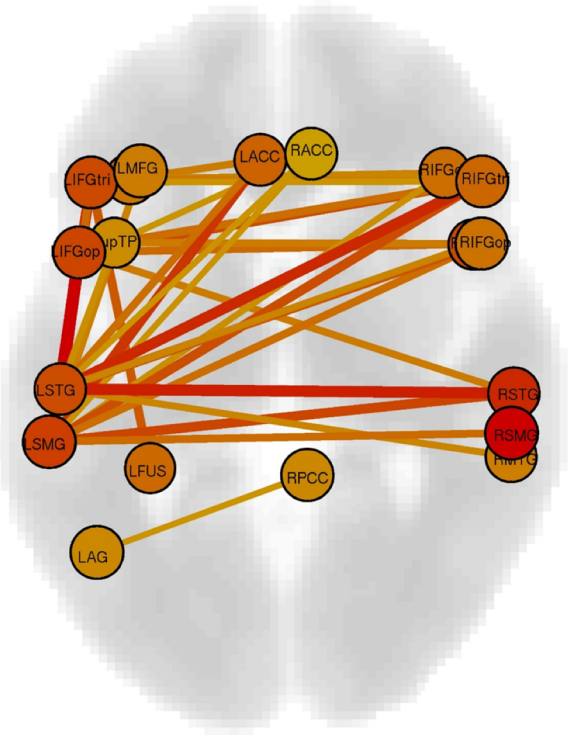
Warm colors = significant positive connections
Cool colors = significant negative connections

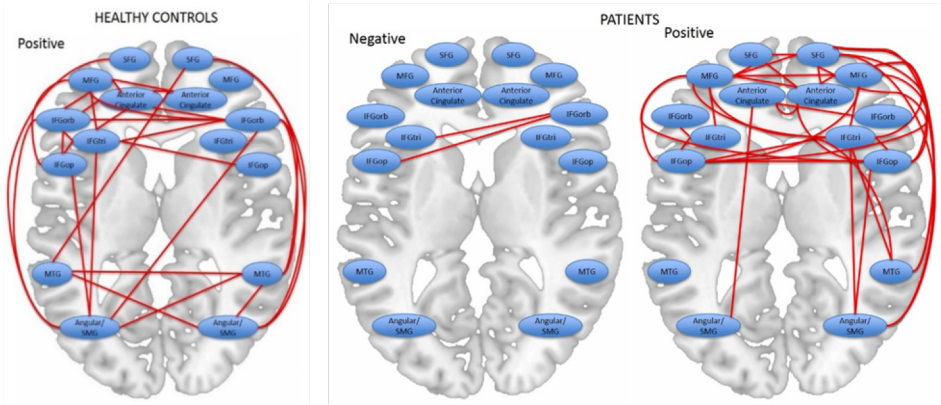
Connections are significant at $p < .05$ after FDR

Warm colors = significantly stronger in controls than PWA
Cool colors = significantly stronger in PWA than controls



Warm colors = significantly stronger in controls than PWA
Cool colors = significantly stronger in PWA than controls





Sims et al. 2016, Neuropsychologia

- Functional Connectivity is reduced in PWA relative to controls, in the language network
- This altered network includes bilateral fronto-temporal regions

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

A combination of TRADITIONAL LANGUAGE REGIONS & DOMAIN GENERAL REGIONS- also participate in recovery

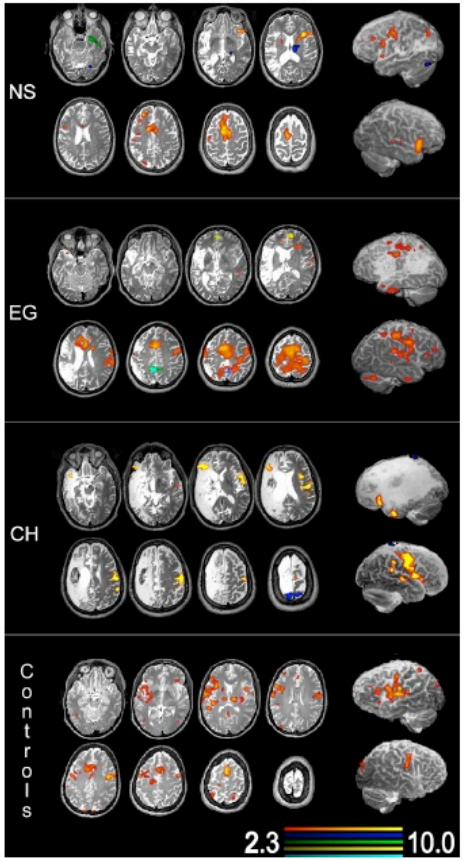
Promoting reorganization

Table 1. Principles of experience-dependent plasticity.

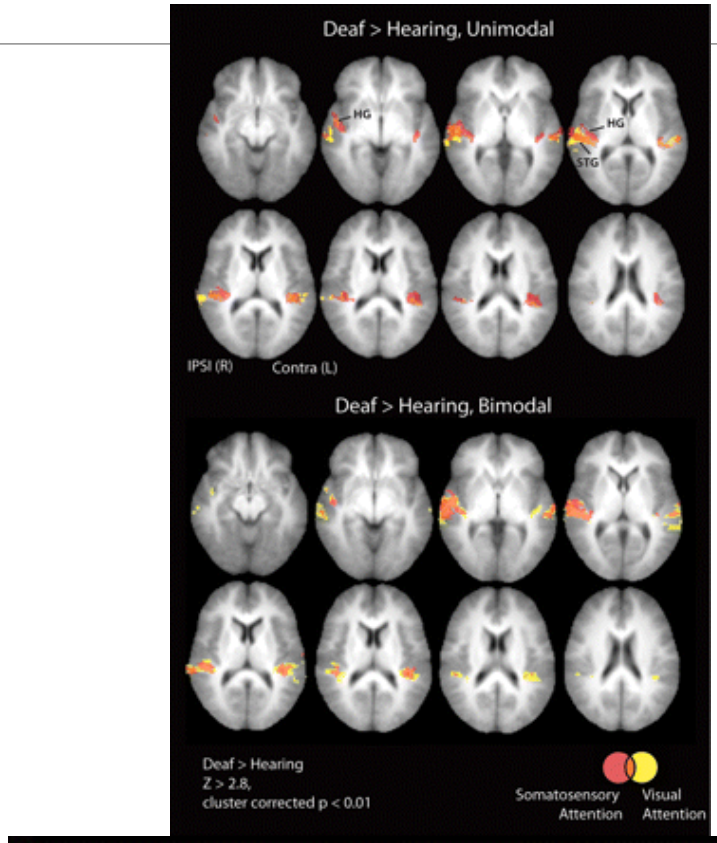
Principle	Description
1. Use It or Lose It	Failure to drive specific brain functions can lead to functional degradation.
2. Use It and Improve It	Training that drives a specific brain function can lead to an enhancement of that function.
3. Specificity	The nature of the training experience dictates the nature of the plasticity.
4. Repetition Matters	Induction of plasticity requires sufficient repetition.
5. Intensity Matters	Induction of plasticity requires sufficient training intensity.
6. Time Matters	Different forms of plasticity occur at different times during training.
7. Salience Matters	The training experience must be sufficiently salient to induce plasticity.
8. Age Matters	Training-induced plasticity occurs more readily in younger brains.
9. Transference	Plasticity in response to one training experience can enhance the acquisition of similar behaviors.
10. Interference	Plasticity in response to one experience can interfere with the acquisition of other behaviors.

Kleim & Jones, 2008, JSLHR

1. Use it or lose it

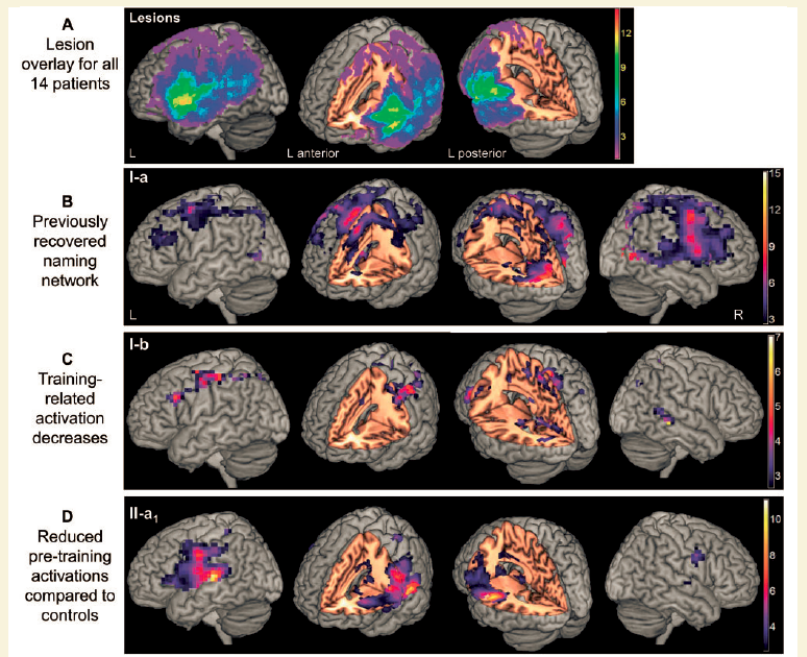


Fridriksson et al. (2007); Neuropsychologia

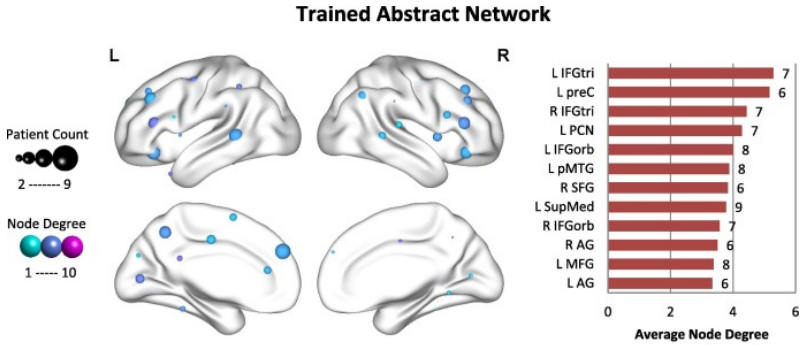


Karns et al., 2012, J neurosciences; Repurposed cortex

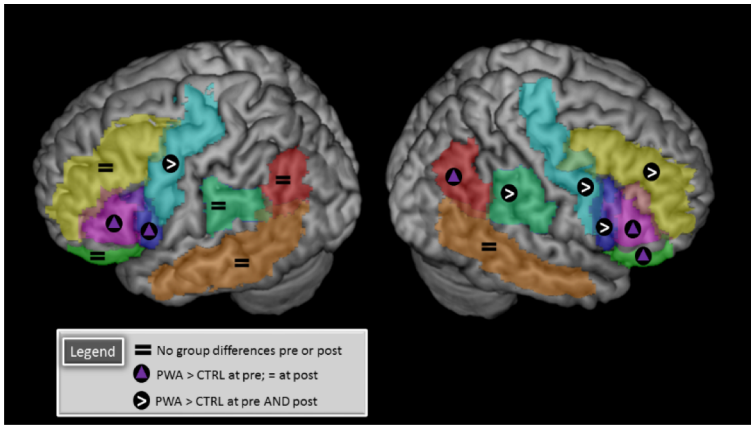
2. Use it and improve it



Abel et al., 2015, Brain



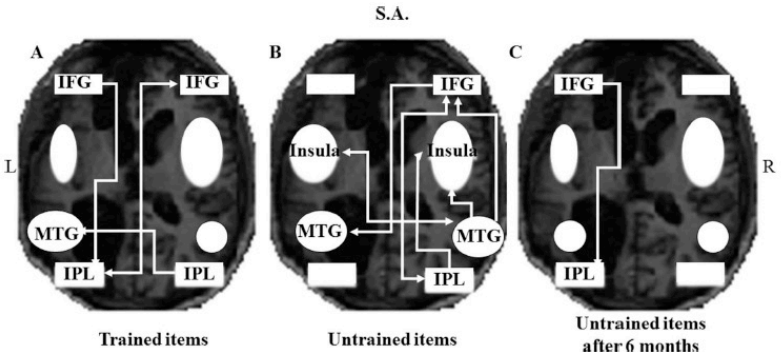
Sandberg et al; 2015, Brain and Language



Johnson et al., under review, (Aphasiology)

3. Specificity, 4. Repetition

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



Vitali et al., 2010, Neurocase

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

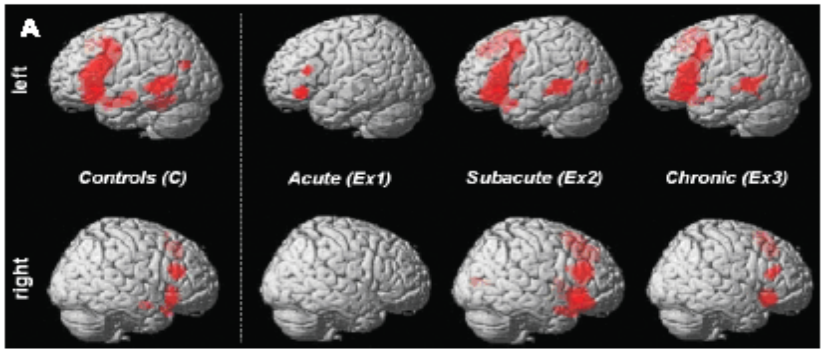
5. Intensity, 6. Time

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
   - Godecke et al., 2012 found that initiating daily aphasia therapy within first 4 weeks post-stroke resulted in better outcomes than usual care.

Godecke, et al. (2012). *International journal of stroke.*



Saur et al., 2006; Brain

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

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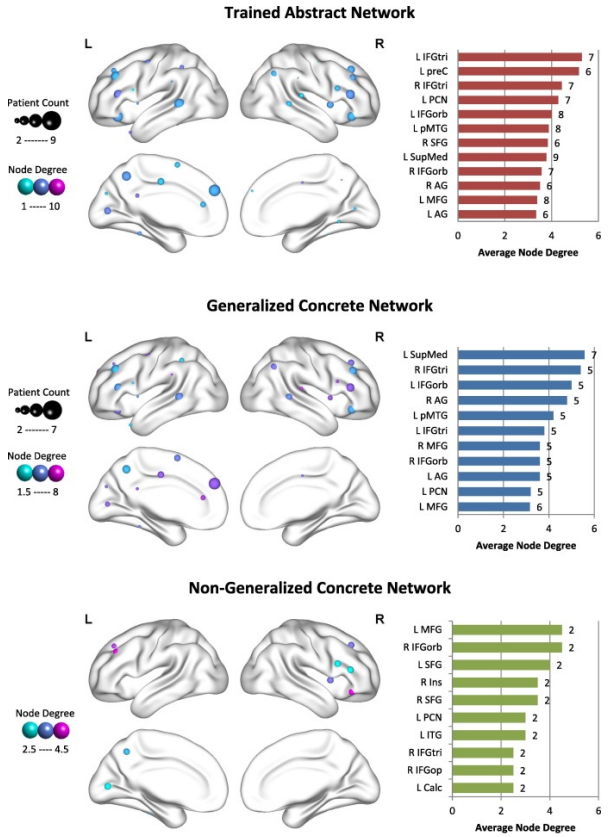
9. Transference
   - Successful and unsuccessful generalization has different consequences in the brain (Sandberg et al., 2015)

10. Interference
   - Maladaptive compensatory strategies (RH)

   - (Rehme et al., Neuroimage 2011)



Sandberg et al; 2015, Brain and Language

Thank you !