Recent Advances in our Understanding of Neuroplasticity of Language Recovery

SWATHI KIRAN, PHD, CCC-SLP
PROFESSOR,
SPEECH AND HEARING SCIENCES,
GRADUATE PROGRAM IN NEUROSCIENCE,
BOSTON UNIVERSITY
ASSISTANT IN NEUROLOGY, MASSACHUSETTS GENERAL HOSPITAL

Disclosure

NIH grants NIDCD/NIH 1P50DC012283; NIDCD/NIH 1K18DC011517; NIH 5F31DC011220

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

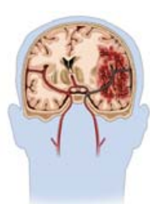
Transneuronal degeneration

Diaschisis

Neurophysiological changes in early recovery

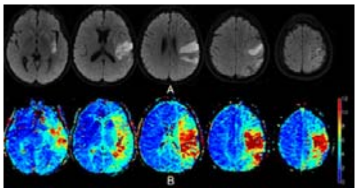
Neurophysiological changes occur in the brain for a period of time following cerebral insult

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

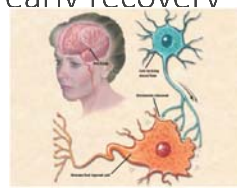


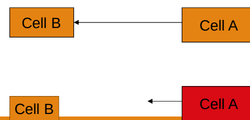
Neurophysiological changes in early recovery

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



Neurophysiological changes in early recovery



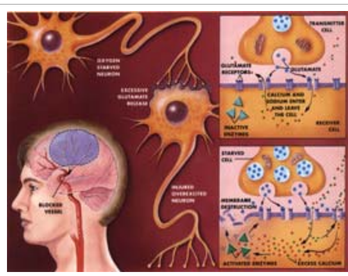


Abnormal concentration /release of neurotransmitters
- occurs immediately after infarction
- Due to ↑ activation/ inhibition after damage to other parts of network
- Neurons release glutamate onto nearby neurons which become excited, overloaded with calcium and die

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

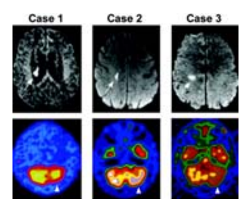
Transneuronal degeneration
- Neurons or nerve cells may atrophy when they don't have normal inputs
- Cell A---Cell B
- Over time B dies without input from A

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

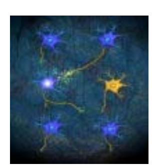
Diaschisis

Repair

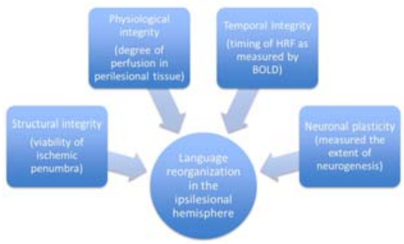
Neuronal regeneration
- Axons and dendrites can regenerate if cell body has remained

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

Promoting repair
- BDNF
- Stimulation



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

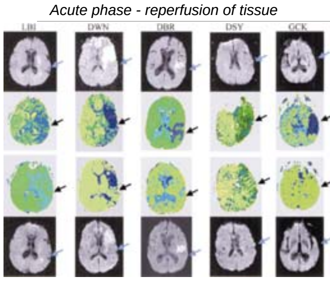


Kiran, 2012; ISRN

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.

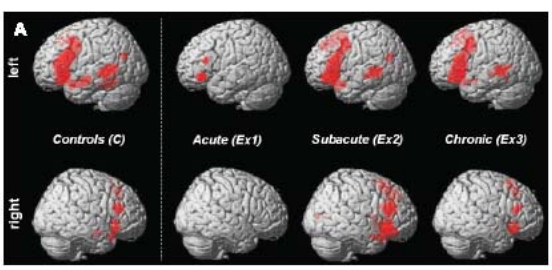
FIG. DWI and PWI scans before treatment (top two rows) and during treatment (lower two rows) for patients who showed improved lexical-semantics with treatment. Arrows point to BA 22.

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

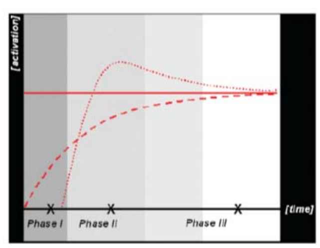


Fig. 5 Model with three phases of language recovery after stroke. Three phases of language recovery: Acute Phase I characterized by loss of function; Subacute Phase II by an upregulation of the language network; Chronic Phase III by a consolidation and normalization of activation. Diagrammed activation 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

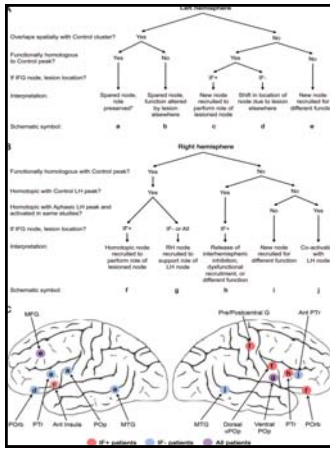
Saur et al., 2006; Brain

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

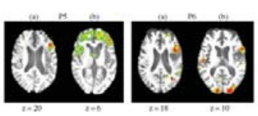
↑ RH participation in language after LH infarction

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

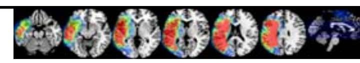
Turkeltaub et al., 2011, Neurology

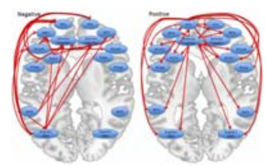
Sebastian & Kiran (2011)- Two tasks

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

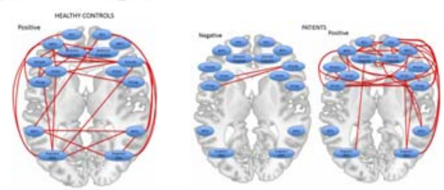


Sebastian & Kiran, 2011; Aphasiology





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.

Sims et al. (2016), Neuropsychologia

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.

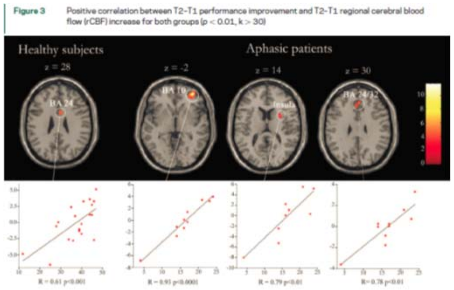
A less efficient but secondary mechanism involves compensation by intrahemispheric neighboring regions in the left hemisphere.

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)

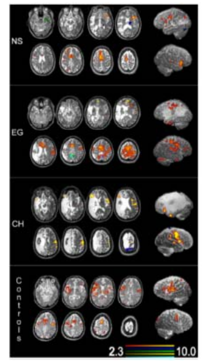
With regards to treatment for word retrieval, imaging studies have shown

Right Hemisphere activation after treatment	Bilateral activation after treatment	Left hemisphere/ perilesional activation after treatment
Peck et al., 2004; Crosson et al., 2005; Meinzer et al., 2006; Raboyeau et al., 2008;	Fridriksson et al., 2006; Fridriksson et al., 2007	Leger et al., 2002; Fridriksson et al., 2010



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.

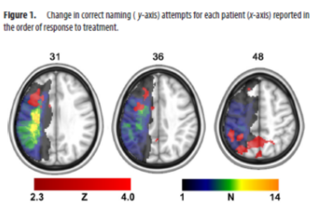
Raboyeau et al., 2008; Neurology



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

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.

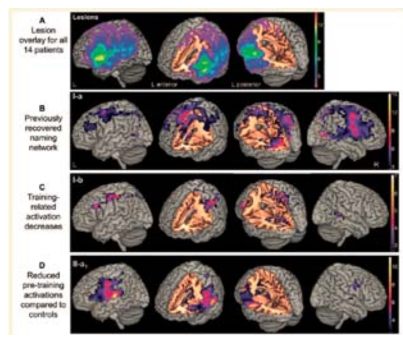
Fridriksson et al. (2007); Neuropsychologia



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



Therapy was associated exclusively with activation decreases, which could mainly be attributed to higher processing efficiency within the naming network.

Abel et al., 2015, Brain

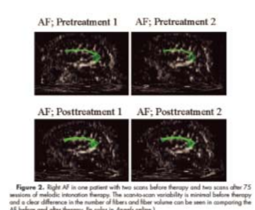
With regards to treatment for word retrieval, imaging studies have shown

Right Hemisphere activation after treatment	Bilateral activation after treatment	Left hemisphere/ perilesional activation after treatment
Peck et al., 2004; Crosson et al., 2005; Meinzer et al., 2006; Raboyeau et al., 2008;	Fridriksson et al., 2006; Fridriksson et al., 2007	Leger et al., 2002; Fridriksson et al., 2010

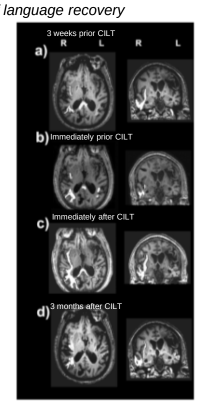
White matter changes as a function of language recovery

29

White matter changes as a function of language recovery



Increase in the number of AF fibers and volume that correlated with behavioral changes (in percent information content units provided) as a function of treatment



Schlaug et al. 2009; ANYAS

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; Meinzer et al., 2006; Raboyeau et al., 2008;	Fridriksson et al., 2006; Fridriksson et al., 2007	Leger et al., 2002; Fridriksson et al., 2010

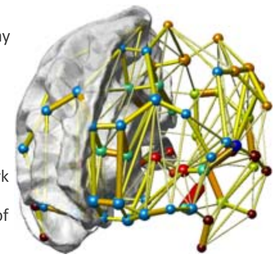
A few studies have examined changes in network connectivity after rehabilitation (Abutalebi et al., 2009; Vitali et al., 2010; Sarasso et al., 2010).

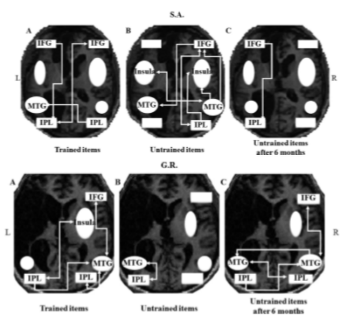
- » Single case(s) studies
- » Show effects of training can be reflected in modulations of connectivity

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.



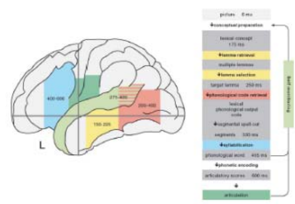


For both patients, more connections that were strengthened appeared during trained items than during untrained items.

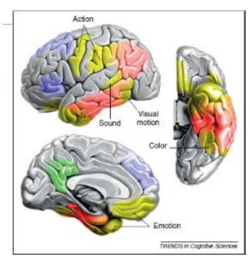
Patient with the larger lesion had more connections strengthened in RH
Patient with the smaller lesion had more connections strengthened in LH

Vitali et al., 2010; Neurocase

Picture naming and semantic feature processing

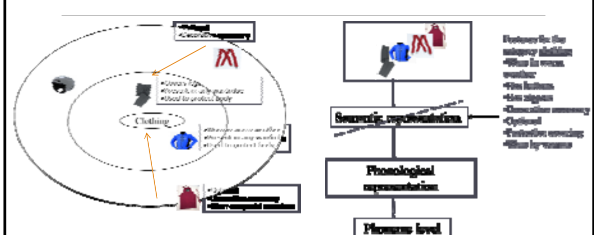


Indefrey & Levelt, 2004, Cognition

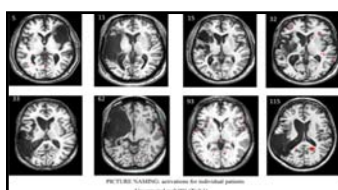


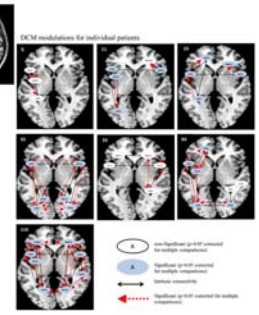
Binder & Desai, 2011 (TICS)

Treatment and generalization based on complexity



Kiran & Thompson, 2003; Kiran, 2007; Kiran & Johnson, 2008; Kiran, 2008, Kiran et al., 2009; Kiran et al., 2011





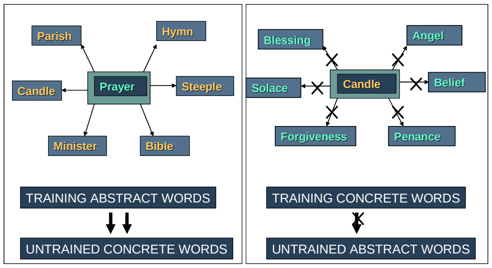
LIFG was the most consistently active VOI in the pre- and post-rehabilitation scans and the most consistently significantly modulated region as a function of rehabilitation

Next, LPCG and RIFG also consistently modulated regions

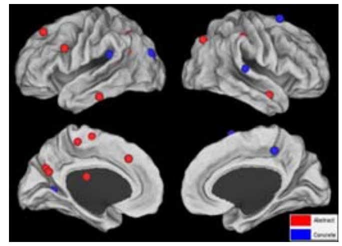
RIFG-RMFG and LIFG-LPCG most consistently modulated connections

Kiran et al; 2015, Frontiers in Human Neuroscience

fMRI of treatment-induced neuroplasticity

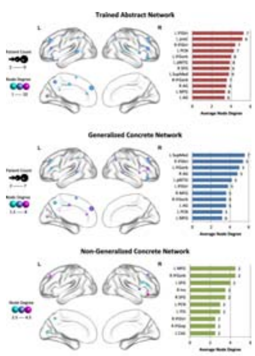


Sandberg et al; 2015, Brain and Language



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).

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)

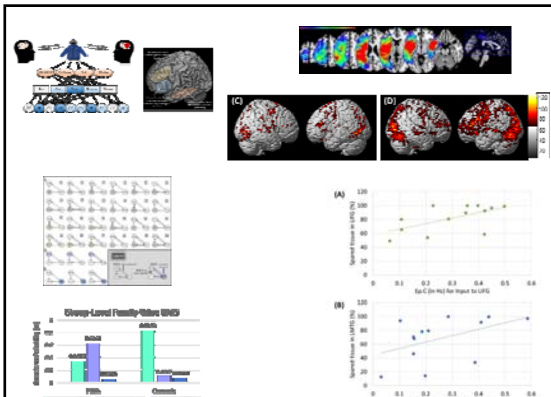
The regions with the highest node degree in the generalized concrete difference network were L SupMed and R IFGtri.

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

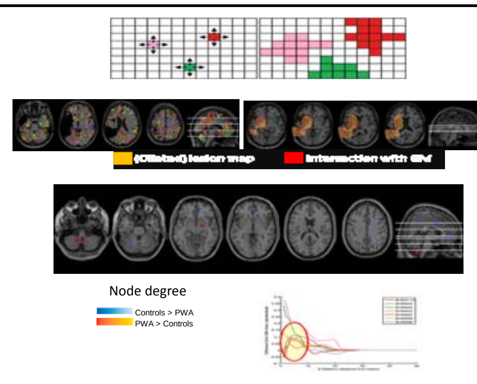
A 'Revised" Summary of fMRI studies

- 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



(A) Correlations between percentage spared tissue and Ep.C values for family #1, shown in green. (B) Correlations between percentage spared tissue and Ep.B values for family #3, shown in blue.

Meier et al., under revision, FIHN



Graph metric analysis of resting state brain networks in post-stroke aphasia –Bohland et al. in preparation

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

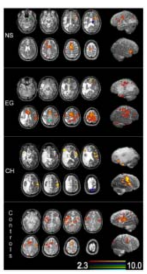
Table 1. Principles of experience-dependent plasticity.

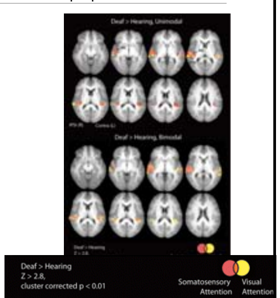
Principle	Description
1. Use It or Lose It	Failure to drive specific brain functions can lead to functional degradation.
2. Use It and Improve It	Training that drives a specific brain function can lead to an enhancement of that function.
3. Specificity	The nature of the training experience dictates the 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

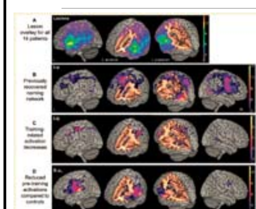
Karns et al., 2012, JNerosciences
Repurposed cortex



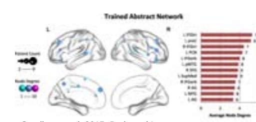


Fridriksson et al. (2007); Neuropsychologia

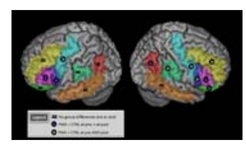
2. Use it and improve it



Abel et al., 2015



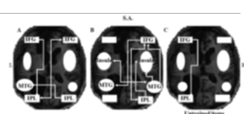
Sandberg et al; 2015, Brain and Language



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

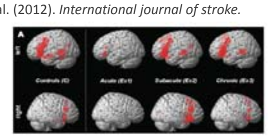
5. Intensity, 6. Time

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

9.

7. Salience, 8. Age, 9. Transference, 10. Interference

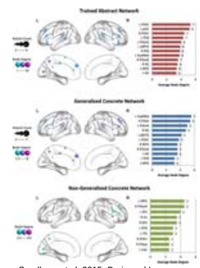
7. Salience matters
  - Attention, motivation, meaning, reward, emotion

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)

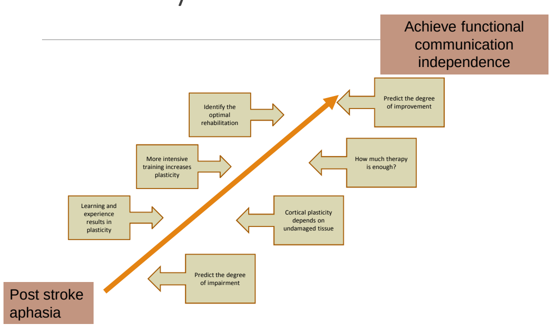
10. Interference
  - Maladaptive compensatory strategies (RH)

  - (Rehme et al., Neuroimage 2011)



Sandberg et al; 2015, Brain and Language

Summary



51

Thank you !

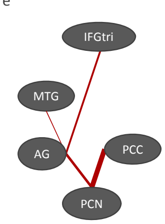
Graph Theoretical Analysis

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

$$k = k_i^{out} + k_i^{in} = \sum_{j \in N} a_{ij} + \sum_{j \in N} a_{ji}$$

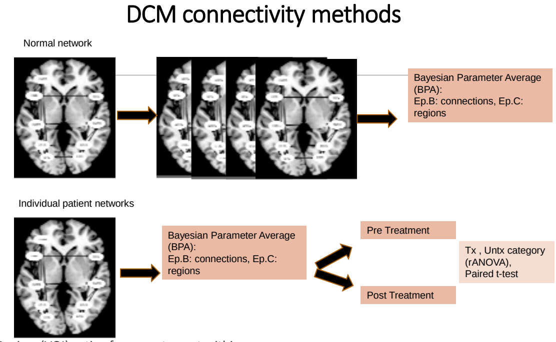
  - AG = 3; PCN = 2



Sandberg et al; 2015, Brain and Language

53

DCM connectivity methods



Regions(VOI) active from pre to post within category for patients

Construct separate model space for each patient

Abutalebi et al., 2009; Kahan & Foltynie, 2013, Seghier et al.,2010; Schofield et al., 2012

54