Understanding and predicting aphasia recovery

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Disclosure

Has significant financial interest
• Scientific Consultant for Constant Therapy/The Learning Corp
• Ownership stock in Constant Therapy

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• Coulter Foundation for Translational Research
• ASHA Foundation Clinical Research Grant
• ASHA Foundation New Century Research Scholars Grant

In the future...

<table>
<thead>
<tr>
<th>Lab/clinic</th>
<th>Neuro-profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social/functional profile</td>
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</tbody>
</table>

| Intensive aphasia therapy & Individual therapy |
| Individual therapy & Social groups |
| Social Groups & Vocational Training |

Predict prognosis and recovery trajectory
Theory of recovery in chronic aphasia

• Hierarchy of recovery with increased damage to the left hemisphere (an updated version of Heiss & Thiel, 2006)
  • Network of regions are activated in the service of language recovery
  • To the extent left hemisphere regions are spared, they are important and engaged in language recovery
  • As damage increases in the left hemisphere, activation shifts to the right hemisphere and multiple demand regions/domain general regions such as MFG
  • The degree to which this network typology instantiates determines the extent of recovery
    • Patients with better/efficient network typology show greater improvement than patients with inefficient typology

Patients with better/efficient network typology show greater improvement than patients with inefficient typology

Language recovery in persons with aphasia (PWA)
Background

T = Treatment Study

INS19,22

PCC22

Not Shown:

ACC19

1. Cao et al., 1999
2. Leger et al., 2002 (T)
3. Perani et al., 2003
4. Fernandez et al., 2004
5. Crosson et al., 2005 (T)
6. Saur et al., 2006
7. Vitali et al., 2007 (T)
8. Meinzer et al., 2008 (T)
9. Fridriksson, 2010 (T)
10. Fridriksson et al., 2010
11. Rochon et al., 2010 (T)
12. Van Oerset al., 2010
14. Szaflarski et al., 2011
15. Allendorfer et al., 2012
16. Szaflarski et al., 2013
17. Van Hees et al., 2014 (T)
18. Sims et al., 2016
19. Nardo et al., 2017 (T)
20. Gold & Kertesz, 2000
21. Meinzer et al., 2006 (T)
22. Raboyeau et al., 2008 (T)
23. Fridriksson et al., 2009
24. Mohr et al., 2014 (T)
25. Skipper-Kallal et al, 2017

Not shown:

medFG10,15
ACC10,15,19
PCUN7,9

12 citations
5-8 citations
<3 citations

Recovery is likely bilateral.

Recovery likely involves a network of regions.
Changes in activation and connectivity after treatment engage a bilateral network but LH IFG is modulated the most.

The more damage to LFG, LMTG and AG/SMG, the higher PSC in bilateral SFG, MFG, and ACC. Bilateral network can serve as an assistive network.

Bilateral network actively engaged during language processing.

Theory of recovery in chronic aphasia

- Hierarchy of recovery with increased damage to the left hemisphere (an updated version of Heiss and Thiel)
  - Network of regions are activated in the service of language recovery.
Participants

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (n = 26)</th>
<th>Untreated Group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - M(SD)</td>
<td>62.8 years (10.2)</td>
<td>59.0 years (11.8)</td>
</tr>
<tr>
<td>Months post-onset - M(SD)</td>
<td>84.3 months (61.6)</td>
<td>85.2 (141.9)</td>
</tr>
<tr>
<td>Sex</td>
<td>17 males, 9 females</td>
<td>10 males</td>
</tr>
</tbody>
</table>

*6 patients completed the study in the untreated group, then crossed over to the treatment group

Which LH and RH gray and white matter regions contribute to recovery?

Normalized T1

Lesion map

Which structural integrity metrics are associated with baseline naming & therapy response?

Without controlling for lesion volume:
- Significant correlations between baseline naming (BNT) and treatment response (PMG) and the majority of LH GM and WM metrics

Controling for lesion volume:
- ONLY significant relationships between BNT and FA in L ILF and L IFOF and
- Between PMG and FA in L ILF and L IFOF remained
The theory of recovery in chronic aphasia

- Hierarchy of recovery with increased damage to the left hemisphere (an updated version of Heiss and Thiel)
  - Network of regions are activated in the service of language recovery
  - To the extent left hemisphere regions are spared, they are important and engaged in language recovery

Left middle temporal gyrus (LMTG)
- Heteromodal semantic processing

Left middle frontal gyrus (LMFG)
- Domain-general cognitive control (e.g., Fedorenko & Thompson-Schill, 2014; Murtha et al., 1999)

Left inferior frontal gyrus (LIFG)
- Controlled retrieval of semantic and/or phonological information (e.g., Indefrey & Levelt, 2004; Thompson-Schill et al., 1997; Wagner et al., 2001)

Frontotemporal connectivity during picture naming

- Participants
  - n = 10 controls (6M; mean age: 61.53 yrs)
  - n = 13 PWA (9M; mean age: 60.66 yrs)

Frontotemporal connectivity during semantic feature judgments

- Participants
  - 21 PWA (17M, mean age = 62.00 ± 11.77 years)
  - 18 healthy controls (10M, mean age = 60.35 ± 10.93 years)
Frontotemporal connectivity during semantic feature judgments

- Greater modulation of LMFG on LIFG for PWA than controls
- Higher fMRI task accuracy and semantic performance related to LpMTG-LIFGtri connections

As damage increases in the left hemisphere, does activation shift to the right hemisphere and multiple demand regions/domain general regions such as MFG?

Adapted from Meier, 2017
Model Space

Family D: Right-lateralized connectivity

Latent extrinsic connections

Task-modulated connections

Model fit in PWA & controls

Family A: Left-lateralized connectivity

Family C: Bilateral, posterior-weighted connectivity

Relationships between lesion, network characteristics & behavior in PWA

Significant interaction of lesion group 2 (anterior damage) by Family C: $\beta = 0.153, t = 2.376, p = 0.019$

PWA with primarily anterior damage – fall within models in Family C: bilateral posterior-weighted connectivity (i.e., anterior damage) than patients with posterior or extensive LH damage
Theory of recovery in chronic aphasia

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Examining language recovery after treatment

Patient timeline

Stage 1 (Pre-treatment)
- Baseline naming evaluation
- Cognitive-linguistic assessment
- Selection of stimuli for fMRI and treatment

Stage 2 (Treatment/No Tx)
- 12 sessions/week
- 42 weeks or 90% accuracy
- 92 weeks without treatment

Stage 3 (Post-treatment)
- Post-treatment naming evaluation

fMRI Scan 1
17 Healthy, age-matched controls
Scanned once on fMRI tasks

Treatment

- Semantic Feature Analysis-based naming treatment

Category Sorting
- Picture Naming
- Review/Analyze Features
- Picture Naming
- Word Generation

Calculate effect size (ES)
(avg. post-tx score - avg. pre-tx score)
(standard deviation of pre-tx score)

Calculate proportional maximal gain (PMG)
(avg. post-tx score - avg. pre-tx score)
(total # of items - avg. pre-tx score)
**Preprocessed functional time series**

**Anatomical ROIs (modified to reflect lesions in PWA)**

**Extract denoised time course in each ROI**

**Pairwise correlations in ROI time series**

**Weighted undirected graph**

**Denoising (regression of confounds: functional outliers, motion, white matter and CSF, main task effects)**

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**Study 1 - Methods**

**Functional connectivity: healthy controls (HC) vs. patients**

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC vs. Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC vs. Untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC vs. Resp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC vs. Nonresp</td>
<td></td>
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</tr>
</tbody>
</table>

*All results sig. after FDR correction for total number of connections*

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**Graph Theory Results: healthy controls (HC) vs. patients**

**Integration:** capability to transmit and combine information from regions throughout the network (Rubinov & Sporns, 2010)

- Network strength
- Network global efficiency

Higher network strength and higher global efficiency are indicative of a more highly connected, highly integrated network

**Segregation:** propensity for the network to support specialized processing "within densely interconnected groups of brain regions" (Rubinov & Sporns, 2010)

- Average clustering coefficient
- Network local efficiency

Higher average clustering coefficient and local efficiency are indicative of a network composed of many specialized clusters that communicate easily amongst themselves
Study design

Patient timeline

Stage 1 (Pre-treatment)
- Baseline naming evaluation
- Cognitive-linguistic assessment
- Selection of stimuli for fMRI and treatment

Stage 2 (Treatment/No Tx)
- 2 sessions/week
- 2 hours/session
- 12 weeks or to > 90% accuracy
- Or 12 weeks without treatment

Stage 3 (Post-treatment)
- Post-treatment naming evaluation

Improvement in treatment (PMG)

Higher network strength ~ higher PMG
Higher global efficiency ~ higher PMG
Larger lesion ~ lower PMG
Older age ~ lower PMG

Higher avg. clustering coef. ~ higher PMG
Higher local efficiency ~ higher PMG
Larger lesion ~ lower PMG
Older age ~ lower PMG

Pre-treatment measures of semantic network integration predicted naming treatment outcomes.
Measures of network segregation predict treatment outcomes (trending significance)
Even after controlling for lesion and age, lower integration and segregation measures associated with poorer naming outcomes.
Local graph measures: responders vs. nonresponders —

Node Strength
Node global efficiency
Node local efficiency

Responders have:
- Higher node strength in LACC, RIFG, RSG
- Higher global efficiency in several LH regions (LAMG, LIFGop), RH regions (RSG, RIFG, RSGop, RAG) and LPCUN
- Higher local node efficiency in RSG

Relative preservation of global and, to a lesser extent, local efficiency may be a biomarker for treatment-related recovery.
Theory of recovery in chronic aphasia

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- The degree to which this network typology instantiates determines the extent of recovery
  - Patients with better/efficient network typology show greater improvement than patients with inefficient typology

Diagram showing:
- Neural markers
- Language markers
- Cognitive markers
- Effective treatments
- Predictive modeling
- Better treatment outcomes, prognosis

Behavioral markers of recovery and plasticity

Vallila-Rohter & Kiran, 2015, JSLHR
Vallila-Rohter & Kiran, 2013, AJSLP
Vallila-Rohter & Kiran, 2013, Neuropsychologia
Villard & Kiran, 2015, Neuropsychologia
Villard & Kiran, 2016, Aphasiology
Villard & Kiran, 2017, Neuropsychologia
Gray & Kiran, 2015, BLC
Gray & Kiran, 2018, BLC
Gilmore et al., UR APMPR
Meier et al., 2015, Aphasiology
Kasdan & Kiran, 2018, JCD
Villard & Kiran, 2013, AJSLP
Kiran & Lebel, 2007, CLP
Sebastian et al., 2012, JNL
Kiran et al., 2007, Aphasiology
Sandberg et al., 2012, JCD
Villard & Kiran, 2012, Neuroradiology
Behavioral markers of recovery and plasticity

- Attention
- Learning
- Control
- EF
- Language
Do pre-treatment non-linguistic cognitive skills predict language treatment gains?

For a 1 point increase in linguistic composite score, PMG increases by 0.23.
For a 1 point increase in non-linguistic composite score, PMG increases by 0.44.

Linguistic and non-linguistic cognitive skills are both important for language treatment success.

Component loadings

<table>
<thead>
<tr>
<th>Executive Functions</th>
<th>Visual/Spatial Memory</th>
<th>Verbal Short-Term Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comp. 1</td>
<td>Comp. 2</td>
<td>Comp. 3</td>
</tr>
</tbody>
</table>
| CLDT Symbol Cancellation | .28          | .79 | -.11
| CLDT Symbol Trails   | .77             | .21 | .33
| CLDT Design Memory   | .02             | .79 | .10
| Code Memory Span     | .21             | .54 | .05
| Digit Span Forward   | .21             | .15 | .91
| Digit Span Backward  | .21             | .06 | .38
| Geometric Inclusion  | .81             | .03 | .31
| Geometric Matching   | .24             | .30 | .09
| PVT F                | .79             | .15 | .28
| Raven's Matrices     | .80             | .30 | .02
| WAB Block Design     | .70             | .26 | .06
Executive function, visual short-term memory and verbal short-term memory significantly predicted treatment outcome and maintenance of gains.
Using algorithms to predict recovery

Which language to treat bilingual patients with aphasia?

Predicting treatment outcomes for bilingual patients with aphasia
Analysis of big data

Patient factors
- Age
- Lesion location
- Lesion size/volume
- Months post stroke
- Education
- Severity of impairment

Treatment factors
- Amount/Intensity of therapy
- Optimal dosage
- Type of treatment
- Therapy setting (home, clinic)

Therapy Outcomes
Clinicians sign up for constant therapy activities.

Patients are assigned therapy tasks.

Patients complete the CT program.

Clinician analyzes data and performance.

Over the span of 4 years (2013-2017), data analyzed for over 20,000 stroke patients.

Patient factors:
- Age
- Lesion location
- Lesion size/volume
- Months post-stroke
- Education
- Severity of impairment

Treatment factors:
- Amount/intensity of therapy
- Optimal dosage
- Type of treatment
- Therapy setting (home, clinic)

Therapy Outcomes
1. With more practice, improvements are between 20-50 points for more severe patients, slightly less for less severe patients, ($F$, $(25, 6904) = 24.5, p < .0001$).

2. More severe patients can achieve high levels of accuracy (80% or higher) with increased practice; ($F$, $(25, 1724) = 26.5, p < .0001$).

How does severity of impairment influence treatment outcomes?

Patient factors:
- Age
- Lesion location
- Lesion size/volume
- Months post-stroke
- Education
- Severity of impairment

Treatment factors:
- Amount/Intensity of therapy
- Optimal dosage
- Type of treatment
- Therapy setting (home, clinic)

Therapy Outcomes

Progress through a domain is represented by a numerical domain score indicating their demonstrated ability level in that skill.
AUDITORY MEMORY DOMAIN

Domain Score Formula:

\[
\text{Domain Score} = \frac{\text{Highest Task Recently Passed}}{\text{Total Tasks in the Domain}} \times 100
\]

If Auditory Command Level 4 is the Highest Task Passed...

\[
\text{Domain Score} = \frac{4}{6} \times 100 = 66.67
\]

Compared the change in domain score over time to their baseline score.

For each domain, analyzed the relationship between the rate of improvement and dosage of therapy.

Linear mixed-effect models examined the association between change from baseline domain score and dosage group.

Model 1 controlled for age, time post-injury, weeks used, and skill domain. Additional models were run for each domain separately.

Post-hoc analyses examined differences between dosage groups.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.000 (0.000)</td>
</tr>
<tr>
<td>Dosage Group (2 Sessions/Week)</td>
<td>0.011 (0.000)</td>
</tr>
<tr>
<td>Dosage Group (3 Sessions/Week)</td>
<td>0.029 (0.000)</td>
</tr>
<tr>
<td>Dosage Group (4 Sessions/Week)</td>
<td>0.026 (0.000)</td>
</tr>
<tr>
<td>Dosage Group (5 or More Sessions/Week)</td>
<td>0.040 (0.000)</td>
</tr>
</tbody>
</table>

Post-hoc analyses revealed significant differences between all dosage groups (p<0.05) except between 3 days/week and 4 days/week.
Population analysis to predict recovery trajectory

Improvements shown by Constant Therapy users in Reading for 5 months:

<table>
<thead>
<tr>
<th>Before Therapy</th>
<th>After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(100 users)</td>
<td>(95% users)</td>
</tr>
<tr>
<td>0 months</td>
<td>0 months</td>
</tr>
<tr>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>2 months</td>
<td>2 months</td>
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<tr>
<td>3 months</td>
<td>3 months</td>
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<tr>
<td>4 months</td>
<td>4 months</td>
</tr>
<tr>
<td>5 months</td>
<td>5 months</td>
</tr>
</tbody>
</table>

Neural Markers

Language/Cognitive Markers

Effective Treatments

Better Treatment outcomes, prognosis

In the future...

Predict progress and recovery trajectory

Neuro-profile

Intensive aphasia therapy & individual therapy

Predict progress and recovery trajectory

Individual therapy & Social groups

Social Groups & Vocational Training

Lab/clinic

Neuro-profile

Predict progress and recovery trajectory

Intensive aphasia therapy & individual therapy

Individual therapy & Social groups

Social Groups & Vocational Training
Thank you to my team

Extra slides—

Bilateral DCM methods overview

- Participants: n=34 PWA and 21 controls (to start; sample reduced for DCM)
- Model space constructed to test hypotheses detailed in hypothesis figure (I can update this figure to include bilateral ITG and send it to you if you want it)
- Final ROIs selected for inclusion in model were regions that were active in the 2nd-level GLMs (one-sample t-tests) in either controls or patients
  - Whole-brain activation in both groups on slide 4
  - Regions included in model space: LMFG and bilateral IFG, MTG and ITG
- Model space shown on slide 5
Activation for contrast of interest: \textit{pics – scr}

\begin{itemize}
\item 2nd-level in controls with no covariates (n=17)
\item 2nd-level in PWA with no covariates (n=34)
\end{itemize}

\begin{itemize}
\item pictures – scrambled
\end{itemize}

\begin{itemize}
\item p < .001, uncorr; cluster extent=5
\end{itemize}

DCM model space

\begin{itemize}
\item Family #1: Left-lateralized connectivity (i.e., “normal” models)
\item Family #2: Bilateral anterior connectivity (i.e., posterior damage models)
\item Family #3: Bilateral posterior connectivity (i.e., anterior damage models)
\item Family #4: Right-lateralized connectivity (i.e., extensive damage models)
\end{itemize}

Bilateral DCM methods overview, cont’d

\begin{itemize}
\item 2nd level activation peaks (next slide) used to create anatomically-constrained bounding masks
\item Slides 8-11 contain all details re: the creation of these masks, in case you want the info
\item Bounding masks shown on slide 12
\item Single-subject peaks within each ROI mask extracted for all participants (VOI overlays shown on slides 13 and 14)
\item Lesion overlay in patient group and percent spared tissue per bounding mask shown on slide 15
\item Model-level inference results (i.e., family-wise BMS) shown on slide 16
\item Note: I’ve renamed these families to describe the connectivity patterns based on feedback from lab folks
\item Parameter-level inference results (i.e., one-sample t-tests on Ep.B values) almost overlaid on slide 17
\end{itemize}
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Activation for contrast of interest: *pics – scr*

- 2nd-level in controls with no covariates (n=17)
  - Activation for contrast: *pictures – scrambled*
  - 
- 2nd-level in PWA with no covariates (n=34)
  - Activation for contrast: *pictures – scrambled*

**Steps of DCM**

1. Define the hypothesis
2. Define other plausible models
3. Estimate models for all subjects
4. Build a DCM model (includes inputs & connections)
5. Define other plausible models
6. Identify effects of interest
7. Inference on parameters (e.g., DCM-B, DCM-C)
8. Extract volumes of interest (VOIs)
9. Family A vs B vs C vs D
10. Determine model fit: Bayesian Model Selection (BMS)
11. PWA rely more on RH intra- & inter-hemispheric connections but specifics depend on site of damage

**Adapted from Seghier et al., 2010**
Bilateral DCM methods overview, cont’d

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- Parameter-level inference results (i.e., one-sample t-tests on Ep.B values) shown on slide 17
1. Identify local maxima for each region from 2nd-level one-sample t-test for pictures – scrambled pictures for PWA & Controls
   - **Patients**
     - LIFGtri: -42 30 -3; t=4.571, cluster size=107; RIFGtri: 42 30 9; t=3.502, cluster size=1
     - LMTG: -42 -69 -18; t=4.804, cluster size=31; RMTG: 51 -72 6; t=3.713, cluster size=1
     - LITG: -48 -51 -12; t=6.647, cluster size=613; RITG: 45 -69 -9; t=8.674, cluster size=408
   - **Controls**
     - LIFGtri: -45 30 9; t=7.863, cluster size=475; RIFGtri: 54 39 12; t=4.69, cluster size=8
     - LMTG: -48 -69 21; t=4.463, cluster size=7
     - LITG: -51 -60 -18; t=8.916, cluster size=654

2. Create bounding boxes surrounding each functional ROI for each group in MarsBar (35x35x35mm for IFG & 35x50x35mm for others)
   - LSFG box anatomically constrained to LSFG+LMFG per AAL atlas

3. Bounding boxes should be anatomically-constrained so that peaks that cross into other regions are excluded
   - First, combine bounding boxes from each group from corresponding regions (e.g., LIFGtri in each group) in MarsBar
     - ROI definition = transform; select both boxes (order does not matter) and use function "r1|r2"
   - Second, combine each bounding box with its corresponding AAL template region so that the area of the bounding box outside the AAL region is kept
     - ROI definition = transform and select the bounding box first and the AAL region second and use "r1 & ~ r2" to combine them
     - This preserves the voxels in r1 (bounding box) that are not in r2 (AAL region)
     - Save this file (e.g., LIFGtri_boxEDGES, RIFGtri_boxEDGES)

4. Obtain the voxels within the bounding box that fall within the anatomical region
   - In MarsBar, combine each bounding box with its corresponding "EDGES" file so that the edges are excluded
     - ROI definition = Transform; select the bounding box first and the "EDGES" file second and use "r1 & ~ r2" to combine them
     - This preserves the voxels in r1 (bounding box) that are not in r2 ("EDGES" file)
     - Save this file (e.g., LIFGtri_bounding_mask)

5. These files are used directly to localize controls’ VOIs
Anatomically-constrained bounding masks

6. For patients, create anatomically-constrained bounding regions that account for the lesion
   • Create the ROIs using the “build_roi” script or via the MarsBar GUI (per the instructions on the lab wiki; instead of using the AAL region, use the Region_Bbox_Anatomical file as your template file)
   • Save this file (e.g., BUMAXX_LIFGtri_Bbox_Anatomical)

7. Masks with lesion deleted used to constrain VOIs selected for patients

Control peaks (n=17, 2 controls excluded)

- LH peaks: All peaks extracted at p < .001 or .01
- RH peaks: All peaks extracted at p < .001 or .01 excluding a noisy VOI in RMTG for 1 control due to lack of activity
Patient peaks (n=30, 4 patients excluded)

- LH peaks: All peaks extracted at p < .001 or .01 excluding noisy VOIs from lesion in LMFG (n=), LIFGtri (n=), LMTG/LAG (n=) or LITG (n=1)
- RH peaks: All peaks extracted at p < .001 or .01 excluding noisy VOIs in RIFGtri (n=), RMTG (n=) or RITG (n=) due to no activation

Patient lesion overlay (n=34)

- LIFGtri % spared: 70.00%
- LITG % spared: 96.61%
- LMFG % spared: 89.19%
- LTPC % spared: 73.29%
- RIFGtri % spared: 99.95%
- RITG % spared: 100.00%
- RMTG % spared: 100.00%

Model inference: Family-wise BMS

- Controls’ best-fit family was family #1 (xp = .95)
  - Single best-fit model was model #4 (xp = .75) followed by model #2 (xp = .15)
- Patients’ best-fit family was family #1 (xp = .57) followed by family #3 (xp = .42)
  - Single best-fit model across the group was model #10 (xp = .53) followed by model #4 (xp = .33)
Baseline structural metrics predicting tx outcomes

Participants

- 30 PWA (20M, 26 right-handed, mean age = 63.0 ± 10.4 years, time post CVA onset = 51.8 ± 49.9 months) participated
- Before therapy, the Western Aphasia Battery-Revised (WAB-R) was used to index overall aphasia severity via the Aphasia Quotient (AQ)
- A 180-item picture naming probe was administered before and after therapy in order to:
  a) characterize pre-treatment naming abilities,
  b) guide treatment assignment and
c) determine the degree of post-treatment naming improvement
Treatment Protocol

- Semantic feature analysis-based treatment was used to target anomia
- Participants were trained on 36 items split between two semantic categories

<table>
<thead>
<tr>
<th>Daily Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category Sorting</td>
</tr>
<tr>
<td>Pretreatment Naming probe</td>
</tr>
<tr>
<td>Press 1 for clothing</td>
</tr>
<tr>
<td>Worn on the feet</td>
</tr>
<tr>
<td>…uh… uh…</td>
</tr>
<tr>
<td>…uh…winter…</td>
</tr>
<tr>
<td>Name as many clothing items as you can that people wear in the winter</td>
</tr>
<tr>
<td>pants…</td>
</tr>
</tbody>
</table>

- Treatment gains were determined by calculating the proportion of potential maximal gain (PMG):

\[ \text{PMG} = \frac{\text{AVG Post-Tx Score} - \text{AVG Pre-Tx Score}}{\text{n of items} - \text{AVG Pre-Tx Score}} \]

MR Acquisition & Processing

- Images acquired on a 3T Siemens Trio Tim scanner with a 20-channel coil
- T1-weighted (TR/TE = 2300/2.91ms, slice thickness = 1mm, 176 sagittal slices), TR-FLAIR (TR/TE = 9000/90ms, slice thickness = 5mm, 35 slices, acceleration x2) and DTI (TR/TE = 900ms/92ms, slice thickness = 2mm, 70 interleaved slices, b = 1000 s/mm²) scans collected

Preprocessing:
- Enantiomorphic replacement of LH lesion using intact RH tissue
- Modified T1 and lesion mask warped to MNI space
- Alignment of original T1 to diffusion scan
- Eddy current correction, rotation of bvectors, and EPI distortion correction
- Diffusion tensor calculated and scalar maps (FA, MD) generated in MNI space

Postprocessing:
- Harvard-Oxford (H-O) cortl-maxprob-thr25 1mm and FMRIB58-FA 1mm templates intersected
- Intersected map resampled to the resolution of DTI outputs
- Final GM & WM masks divided into ROIs
- ROI masks multiplied by each patient's FA map
- Mean FA and MD extracted from WM adjacent to bilateral ROIs: ACC, AG, IFG, ITG, MFG, MTG, SFG, and SMG
- Percentage of spared tissue calculated in cortical ROIs (GM %sp) and WM adjacent to cortical ROIs (WM %sp)

Results: PCA loadings

Four components resulted from the PCA including all LH WM metrics (i.e., FA, MD and spared tissue)

Metrics from adjacent LH regions tended to load together
Results: PCA loadings

Three components resulted from the PCA including RH diffusion metrics.

Variables loaded onto components by type (i.e., MD vs. FA).

Positive
Negative

Three components resulted from the PCA including spared cortical tissue.

Highly-damaged, canonical perisylvian language regions loaded together (excluding ventral temporal regions).

Most spared regions (LACC, LMFG, LSFG) loaded separately.

Factor loading scores were extracted from all WM and GM components.

Component predictors plus lesion volume were entered into backward stepwise regression models to determine final multi-modality regression models.
Results: Language predictions

**Baseline aphasia severity**

- Higher WAB AQ (i.e., less severe aphasia) was related to greater integrity of bilateral ROIs

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.39</td>
<td>0.06</td>
<td>3.52</td>
</tr>
<tr>
<td>LH Med Damaged</td>
<td>-0.13</td>
<td>0.08</td>
<td>-1.63</td>
</tr>
<tr>
<td>LH PFC Diffusion</td>
<td>-0.10</td>
<td>0.06</td>
<td>-1.66</td>
</tr>
<tr>
<td>LIFG &amp; LFG</td>
<td>-0.06</td>
<td>0.06</td>
<td>-0.95</td>
</tr>
<tr>
<td>RH Med</td>
<td>-0.13</td>
<td>0.07</td>
<td>-1.96</td>
</tr>
<tr>
<td>RH PFC Diffusion</td>
<td>-0.10</td>
<td>0.07</td>
<td>-1.45</td>
</tr>
<tr>
<td>LH Med &amp; PFC Diffusion</td>
<td>-0.22</td>
<td>0.10</td>
<td>-2.17</td>
</tr>
</tbody>
</table>

**Baseline naming abilities**

- Compared to the AQ model, fewer structural metrics were predictive of baseline naming
- Better pre-treatment naming was associated with higher anisotropy of LH prefrontal ROIs

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.78</td>
<td>0.53</td>
<td>-1.47</td>
</tr>
<tr>
<td>LH PFC Diffusion</td>
<td>-0.34</td>
<td>0.23</td>
<td>-1.48</td>
</tr>
<tr>
<td>LIFG &amp; LFG</td>
<td>-0.66</td>
<td>0.33</td>
<td>-2.01</td>
</tr>
<tr>
<td>RH Med</td>
<td>-0.66</td>
<td>0.33</td>
<td>-2.01</td>
</tr>
<tr>
<td>Lesion Volume</td>
<td>-2.00</td>
<td>1.00</td>
<td>-2.00</td>
</tr>
</tbody>
</table>

**Naming treatment outcomes**

Significant predictors of treatment-related naming improvements included baseline integrity of LH prefrontal (i.e., LIFG, LMFG, LSGF, LACC) and ventral temporal regions

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.499</td>
<td>0.047</td>
<td>10.67</td>
</tr>
<tr>
<td>LH PFC Diffusion</td>
<td>-0.21</td>
<td>0.07</td>
<td>-3.00</td>
</tr>
<tr>
<td>LIFG &amp; LFG</td>
<td>0.169</td>
<td>0.056</td>
<td>3.07</td>
</tr>
<tr>
<td>RH Med</td>
<td>-0.399</td>
<td>0.052</td>
<td>-7.37</td>
</tr>
<tr>
<td>LH Med Damaged</td>
<td>-0.494</td>
<td>0.140</td>
<td>-3.53</td>
</tr>
</tbody>
</table>

*Adjusted R-squared = 0.669
fMRI Tasks

<table>
<thead>
<tr>
<th>Picture naming</th>
<th>Semantic feature judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Picture 1" /></td>
<td><img src="image2.png" alt="Picture 2" /></td>
</tr>
</tbody>
</table>

Functional Connectivity in Patients

- FC is reduced in patients with neurological damage relative to controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Increased Connectivity</th>
<th>Trend Toward Typical FC</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abutalebi et al., 2009</td>
<td>LH naming and language control network</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarasso et al., 2010*</td>
<td>LH language areas only</td>
<td></td>
<td>RH become less control-like</td>
</tr>
<tr>
<td>Vitali et al., 2010*</td>
<td>Bilateral naming network</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mancho et al., 2013</td>
<td>Posterior DMN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Hees et al., 2014</td>
<td>LMTG/LSTG, LIFG, RMTG/RSTG, LSPG, LSPG</td>
<td>Pre-to differences b/w PWA &amp; controls were not present at points</td>
<td></td>
</tr>
<tr>
<td>Kiran et al., 2015*</td>
<td>Bilateral IFG and LMFG were modulated by treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandberg et al., 2015*</td>
<td>Trained (abstract) and untrained (concrete) networks</td>
<td>Node degree increased in LIFG (abstract network) and L superior medial gyrus and RSTG (concrete network)</td>
<td></td>
</tr>
<tr>
<td>Duncan &amp; Smell, 2016</td>
<td></td>
<td>Functional modularity (segregation) Increased</td>
<td></td>
</tr>
</tbody>
</table>

Green text indicates task-based study

Blue text indicates resting-state study

*Study examined effective connectivity
FC Methods

Participants:
- 26 PWA who completed treatment
  - Age: M = 63.0, SD = 10.2 years
  - MPO: M = 58.2, SD = 51.8 months
  - 17 healthy controls
    - Age: M = 60.0, SD = 10.8 years
    - 11 male, 6 female
- 17 male, 9 female

ROI Specification
- 38 ROIs based on naming literature
- Standard ROIs from AAL Atlas for Healthy control ROIs and patient RH ROIs
- Individualized LH ROIs for patients to account for lesion

fMRI task

Additional Preprocessing and Denoising
- Identified global signal and motion outliers in functional data (ART Toolbox)
- Identified confounds in BOLD signal associated with physiological noise based on WM and CSF masks (CompCor method, Behzadi et al., 2007)
- Linear regression & high-pass filtering to remove WM/CSF components, motion parameters, scrubbing, and main effect of task conditions

First-level analysis
- At subject-level, GLM to estimate pairwise Pearson correlations in BOLD time series between all ROIs, weighted by HRF-convolved signal for each condition

Second-level analysis
- One-sample t-tests:
  - Controls
  - PWA pre-tx
- Two-sample t-tests:
  - Controls vs. PWA pre-tx
  - Controls vs. PWA post-tx

• Inputs: stimulus functions → experimental manipulations
• State variables: neuronal and neurophysiological variables that are required to form outputs
• Outputs: hemodynamic responses (in fMRI experiments)

DCM models 5 state variables for each region of interest:
- 4 variables correspond to a hemodynamic model
- The first (and most important) corresponds to neuronal activity

DCM: Dynamic Causal Modelling

Friston, Harrison, & Penny, 2003; Friston, Mechelli, Turner, & Price, 2000
**Neuronal state equation**

\[ z = F(z, u, \theta) \]

- **F**: function describing neurophysiological influences on activity
- **z**: activity
- **u**: inputs
- **\( \theta \)**: parameters of the model

\[ \frac{dz}{dt} = (A + \sum_{j} B_j)z + Cu \]

- **A**: Intrinsic coupling between regions
- **B**: Change in coupling induced by jth input
- **C**: Extrinsic influences of inputs on activity

---

**Regions implicated in naming and its component processes**

- Bilateral (but LH dominant) perisylvian network recruited for naming
  - Ventral semantic regions
  - Dorsal phonological regions
- Graded specialization in temporal lobe
  - ATL (or Wernicke's): conceptual processing across modalities
  - Ant-mid MTG: lexical-semantic processing
  - pMTG: lexical-semantic processing or semantic control
  - IFG critical for naming & semantic control
- Role of AG unclear?

---

**PWA**

- **n = 35** participants, aged 18-89 years
- Inclusionary criteria:
  - Absence of psychiatric, other neurological, or active medical conditions
  - Primary language of English
  - Normal/corrected-to-normal vision & hearing
  - Presence of anomia
- Exclusionary criteria:
  - RH or multiple LH infarcts
  - Time post-stroke < 6 months

---

**Controls**

- **n = 20** age-matched, neurologically-intact individuals
- Inclusionary criteria: same as PWA (excluding anomia)
Behavioral Assessments

Global cognitive skills:
- Western Aphasia Battery-Revised (WAB-R) (Kertesz, 2007)
- Cognitive-Linguistic Quick Test (CLQT) (Helm-Estabrooks, 2001)

Naming skills:
- Boston Naming Test (BNT) (Kaplan, Goodglass, Weintraub, Segal, & van Loon-Vervoorn, 2001)
- 180-item picture naming probe
- Anomia determined by ≤ 75% accuracy

Semantic skills:
- PALPA 51: Word Semantic Association (Kay, Colheart, & Lesser, 1992)
- Pyramids & Palm Tree (PAPT) (Howard & Patterson, 1992)
- Nonstandardized behavioral tasks (Meier, Lo, & Kiran, 2016)

fMRI Data Collection and Preprocessing

- Scan information
  - Siemens 3T Trio Tim scanner
  - 20-channel head and neck coil
  - T1 images
    - 1.7mm slice size
    - 1 mm3 voxels
    - TR = 1300 ms
  - BOLD functional images
    - 40 axial slices
    - 2.25 x 2.25 x 3 mm voxels
    - TR = 2500 ms

- General Preprocessing
  - Motion correction
  - Spatial normalization
  - Detection of functional outliers with ART
  - Denoising: remove confounds in BOLD signal associated with physiological noise (CompCor method), bad volumes, motion, and main effects of conditions
• Aim of DCM is to estimate and make inferences about how coupling among brain regions is influenced by experimental tasks
• DCM is...
  o Dynamic: Differential equations are used to model inter-regional interactions
  o Causal: DCM describe how dynamics in one neuronal population influence dynamics in another
  o Interpretable from a neurophysiological perspective: DCM is hypothesis-driven and constrained by an underlying biological model
  o Bayesian: Models and parameters are constrained by their prior distribution

Participants

• Patient group
  • 30 adults with aphasia
  • Inclusion:
    • Aphasia due to left-hemisphere stroke
    • Onset of aphasia > 6 months before enrollment (i.e., chronic PWA only)
    • Performance below 70% on 180-item picture naming assessment
  • Exclusion:
    • History of multiple stroke events
    • Neurological trauma or disease other than stroke
    • Unsafe for scanning in MRI

• Control group
  • 16 older adults age-matched to PWA

Study design

Patient timeline

• Pre-Treatment
  • 180 item picture naming battery (x3)
  • Klamü assignment

• Treatment
  • SFA-based training
  • 2 sessions/week
  • 2 hours/session
  • Weekly naming probes
  • 12 weeks or > 90% accuracy

• Post-Treatment
  • Re-administration of confrontation naming battery (x3)
  • Cognitive-linguistic testing

Healthy controls
• Scanned once on fMRI tasks
• Assigned “trained” categories comparable to those of PWA

*Includes Western Aphasia Battery to determine overall aphasia severity (Aphasia Quotient)
Stimuli

• Based on naming performance, PWA are assigned the following stimuli sets:
  1. Treated
     • 36 items total, 18 from each of two semantic categories
     • Targeted during treatment sessions, presented during weekly naming probes and in fMRI tasks
  2. Untreated/related
     • 36 items total, 18 each from the categories on which a patient is trained
     • Presented during weekly naming probes and in fMRI tasks
  3. Untreated/unrelated
     • 36 items total, all from a category on which the patient is NOT trained
     • Presented during weekly naming probes only
  4. Control set
     • 36 items, all from the category fruit
     • Assessed at pre- and post-treatment and in fMRI tasks, but not during weekly naming probes

Treatment

• Semantic Feature Analysis-based naming treatment

Treatment gains determined by calculating the proportion of potential maximal gain (PMG):

\[
\frac{(AVG\ Post-Tx\ Score - AVG\ Pre-Tx\ Score)}{(n\ of\ items - AVG\ Pre-Tx\ Score)}
\]

What is the optimal dosage of treatment for aphasia?

SAMPLE DOMAIN: Auditory Memory

HEALTHY ADULTS (MTURK)  STROKE PERFORMANCE
SAMPLE DOMAIN: Auditory Memory

Domain Score Formula:
Highest Task Recently Passed
Total Tasks in the Domain

If this is the highest task passed
Domain Score: 0 / 17 = 0% mastered

Domain Score Calculation

- Task 5
- Task 4
- Task 3
- Task 2
- Task 1

Day 1
Task 3
Failed
Task 2
Passed
Task 1
Failed

Day 2
Task 3
Failed
Task 2
Passed

Day 3
Task 3
Passed

Day 4
Task 4
Passed

Day 5
Failed

Current Domain Score: 3 / 5

Domain Score Calculation

Aphasia affects approximately one-third of stroke survivors and persists in about 15% of persons with aphasia (PWA)

- Age
- Length of hospitalization
- Lesion size
- Hemiplegia at discharge
- Gender
- Type of stroke
- Side of lesion
- Initial severity of language impairment
- Education

Flowers et al., 2016; Laska et al., 2001; Lazar et al., 2008; Pedersen et al., 1995; Plowman et al., 2012; Wade et al., 1986
Aphasia affects approximately one-third of stroke survivors and persists in about 15% of persons with aphasia (PWA).

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. But also, LPCG and RIFG consistently modulated regions.

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

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
Structural predictors

**Participants**
- 30 PWA (20M, 26 right-handed; mean age = 63.0 years; time post CVA onset = 51.8 months)
- At baseline, underwent T1 and DTI scans and behavioral assessment
- Completed up to 12 weeks of semantic feature analysis-based treatment (Oulwek, 2 hours/session)

**MR data processing**
- NINDA DTI preprocessing pipeline* used that included additional steps to account for lesion
- Harvard-Oxford (H-O) cortl-maxprob-thr25 1mm and FMRIB58-FA 1mm templates intersected
- Intersected map resampled to the resolution of DTI outputs
- Final GM & WM masks* divided into ROIs
- ROI masks multiplied by each patient's FA map
- Mean FA and MD extracted from WM adjacent to bilateral ROIs: ACC, AG, IFG, ITG, MFG, MTG, SFG, and SMG
- Percentage of spared tissue calculated in cortical ROIs (GM %sp) and WM adjacent to cortical ROIs (WM %sp)

<table>
<thead>
<tr>
<th>ROI</th>
<th>GM %sp</th>
<th>WM %sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFG</td>
<td>71.20</td>
<td>76.78</td>
</tr>
<tr>
<td>LMFG</td>
<td>71.36</td>
<td>85.84</td>
</tr>
<tr>
<td>LSFG</td>
<td>88.52</td>
<td>96.99</td>
</tr>
<tr>
<td>LACC</td>
<td>97.70</td>
<td>99.56</td>
</tr>
<tr>
<td>LSTG</td>
<td>51.06</td>
<td>52.93</td>
</tr>
<tr>
<td>LMTG</td>
<td>68.46</td>
<td>75.35</td>
</tr>
<tr>
<td>LITG</td>
<td>83.14</td>
<td>95.57</td>
</tr>
<tr>
<td>LAG</td>
<td>60.43</td>
<td>65.38</td>
</tr>
<tr>
<td>LSMG</td>
<td>54.22</td>
<td>60.72</td>
</tr>
</tbody>
</table>