Three Approaches to Addressing Lesioned Tissue in Graph Theory Neuroimaging Analyses for Individuals with Stroke

COBALT
COGNITION, BRAIN AND LANGUAGE TEAM

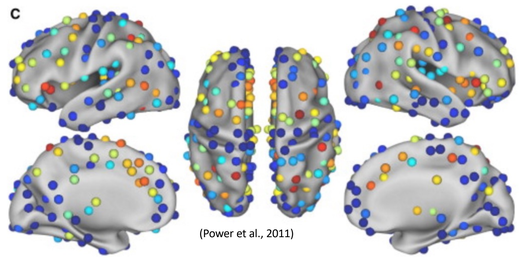
Rachel Langer[1], Advisor: Amy E. Ramage[2]

[1]Department of Neuroscience & Behavior, [2]Communication Sciences and Disorders, University of New Hampshire, Durham, NH

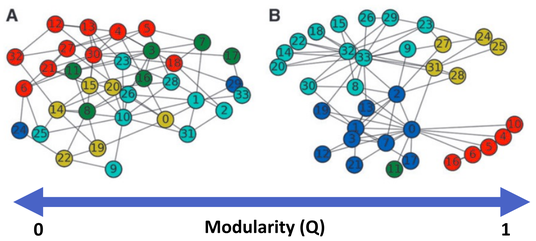
Background

Stroke results from disruptions in blood flow to the brain that leads to damage of neural tissue in the areas deprived of blood flow. These damaged areas become know as lesions, which cause whole brain system disruptions in structural and functional connectivity. Structural and functional connectivity can be quantified with graph theory metrics, that utilize functional MRI (fMRI) images to create a functional connectome of the whole brain.

Graph theory - defines brain regions into **nodes** and their connections between them as **edges** (Tao et al., 2020)



Modularity, or Q, is one such graph theory metric that can quantify changes in functional connectivity post-stroke. It is a whole brain measure that determines the segregation and integration of groups of nodes, known as modules (Tao et al., 2020). It is a calculation based on the maximum possible number of links of nodes within modules and the minimum possible number of links between modules (Rubinov & Sporns, 2010).



Two graphs that visualize differences in modularity (Q). Graph B has higher modularity (more segregation of nodes) than Graph A (Duncan & Small, 2016). The colors indicate modules.

Why is Modularity Important?

- Predictor of treatment outcomes – individuals post left hemisphere stroke had higher modularity as a result of treatment (Duncan & Small, 2016; Tao & Rapp, 2019)
- Biomarker for brain plasticity and adaptation (Gallen & D'Esposito, 2019)

Differences in protocols for lesion identification and segmentation in fMRI stroke studies leads to variability in results. It has been proposed that the the most common method of lesion identification in fMRI, known as lesion network mapping (LNM), disregards the effect of both subcortical and white matter damage when creating regions of interest (ROIs). Most other methods simply exclude nodes that correspond to lesioned tissue when calculating graph theory analyses.

This study seeks to investigate how a whole brain functional connectivity measure, such as Q, is influenced by treating lesioned tissue with three differing approaches.

Contact info:
Rachel Langer
Rachel.langer@unh.edu
Dr. Amy Ramage
Amy.Ramage@unh.edu

Research Questions & Hypotheses

How does (1) including lesioned nodes, (2) using binary lesion masks for lesioned nodes, or (3) using random time series for lesioned nodes influence Q?

Hypothesis: We hypothesized that Q will be most influenced by treating lesioned nodes with binary lesion masks, as inputting zeroes into the blood-oxygen-level-dependent (BOLD) signal of the nodes is most different from including the originally collected data or from utilizing random time series.

How does (1) including lesioned nodes, (2) using binary lesion masks for lesioned nodes, or (3) using random time series for lesioned nodes influence the relationships between Q and individual lesion volumes and aphasia severity?

Hypothesis: We hypothesized that the relationship between Q, individual lesion volumes, and aphasia severity would be most influenced using binary lesion masks for lesioned nodes.

Participants

48 individuals from Sydney, Australia participated in this study. 30 individuals had suffered a left-hemisphere stroke and aphasia (PWA) and 18 individuals were healthy, age-matched controls (HC).

- Lesion volume, age, months post onset of stroke, and apraxia of speech (AOS) severity were also determined for each subject.
- Majority of the PWA subjects showed damage to 50% of nodes in the subcortical brain network outlined by the Power et al. atlas (2011).
- All PWA underwent speech and language testing (Western Aphasia Battery- Revised) to diagnose and determine their aphasia severity.

	Stroke	Control
n	30	18
Age	62.7 ± 10	62.6 ± 9
Sex*	25M	8M
Months post Onset	40.3 ± 40	
Education (years)	14.7 ± 3	
Lesion Volume (mm)	96.7 ± 76	
Q (regular)	0.453 ± 0.09	0.451 ± 0.10
Q (random)	0.432 ± 0.09	

More males in the stroke group than the control ($\chi^2_{1,47} = 9.26$, $p = 0.002$)

Method

Voxel based morphometry (VBM) was analyzed from each subject's T1 structural images to determine which nodes were lesioned. VBM measures the percentage of gray matter left in a particular voxel, or node. A node was considered lesioned if <25% of gray matter was present (Tao & Rapp, 2019; Tao & Rapp, 2020; Tao & Rapp, 2021).

Three Approaches

Three different approaches were taken to alter the resting state fMRI (rsfMRI) BOLD signals for each subject in order to determine their influence on Q.

1. Including Lesioned Nodes ($Q_{regular}$) - The original resting state BOLD signals.
2. Binary Lesion Mask (Q_{binary}) - The 216 BOLD signals for each of the lesioned nodes were changed to zero.
3. Random Time Series (Q_{random}) - 216 random numbers, with a mean of 1000, was input into the 216 images for each lesioned node for each subject.

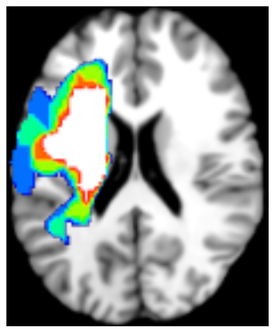


Image Acquisition and Processing

Participants underwent resting state fMRI imaging utilizing a Philips 3T TX MRI scanner. T1-weighted volumetric images for each subject was also was acquired. Blood-oxygen-level-dependent (BOLD) contrast for a 9-min continuous scan was utilized to acquire a total of 216 resting-state echo-planar images.

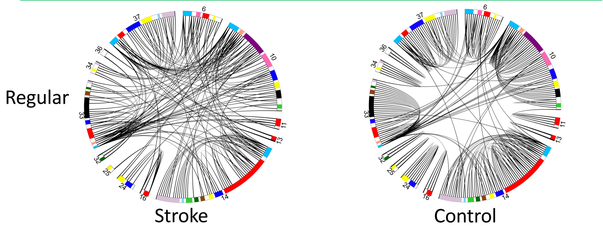
Image preprocessing: Time series for all 264 Power atlas nodes were extracted. Mean time series for each node was correlated with each other node to create a 264 x 264 connectivity matrix.

Modularity (Q) was calculated in MATLAB (BCT, Rubinov & Sporns, 2010) using the correlation matrices to acquire whole-brain community relationships. Analysis provided partitions (modules) and Q values for each subject.

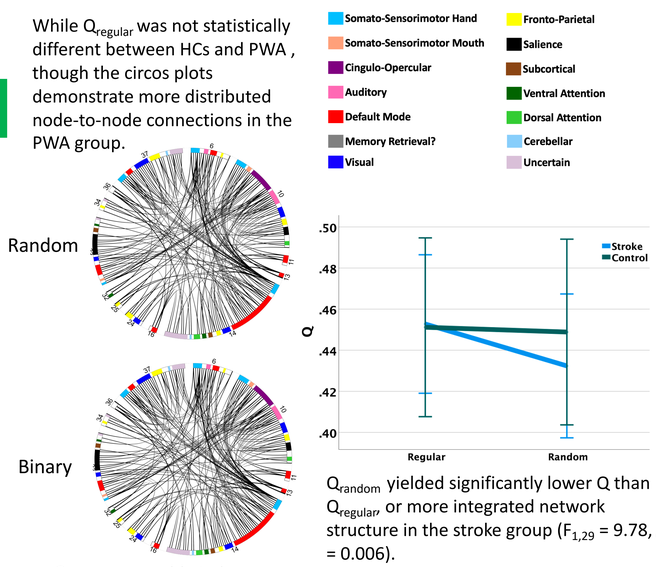
Data Analysis

- Independent samples t-tests were used to compare PWA vs. HCs for age and a chi-square test to determine gender differences by group.
- Spearman correlations between Q or Q_{random} and age, months post onset of stroke, WAB aphasia quotient, and WAB subtest scores were calculated, and significance was established at rho > |0.30|, $p < 0.05$.
- Circle plots were created by using the average subject matrix from the modularity scripts on all subjects to run modularity on it again to get a standard number of modular partitions across groups. Matrices for either PWA regular, PWA binary, or PWA random to plot.

Results



While $Q_{regular}$ was not statistically different between HCs and PWA , though the circos plots demonstrate more distributed node-to-node connections in the PWA group.

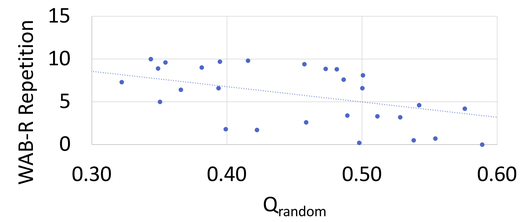


Q_{binary} was unable to be calculated with the MATLAB script, but a circle plot was able to be created.

Q_{random} yielded significantly lower Q than $Q_{regular}$, or more integrated network structure in the stroke group ($F_{1,29} = 9.78$, $p = 0.006$).

Results Continued

- No correlation was found between lesion volume or aphasia severity and Q.
- There was a negative correlation between Q_{random} and WAB Repetition, which is a subtest of the WAB ($R^2 = 0.213$).



Conclusions

- None of the approaches taken to treat lesioned nodes influenced Q enough for it to be concluded that ignoring lesions is not the best approach.
- The negative correlation between Q and WAB repetition may be explained by the Dual Stream Model proposed by Hickok & Poeppel (2007). This model can describe that repetition is dependent on integration of both the ventral and dorsal streams, meaning that it would be most impacted by expansive damage to the brain, like in stroke.

Study Limitations & Future Directions

Limitations

- MATLAB was unable to calculate Q values for binary masking of lesioned nodes, so we were not able to determine if Q_{binary} showed a statistically significant difference when compared to Q_{random} or $Q_{regular}$.
- The small sample size in this study might also explain why there were minimal statistically significant results.

Future Directions

- Compare the effects of the three differing methods while calculating another graph theory metric with this data, known as degree centrality (DC). DC quantifies the importance of each node within the brain network by determining its transmission capabilities (Min et al., 2023).
- Utilize different methodology to identify lesions that may be more accurate. One such method, known as functional disconnection, was proposed by Souter et al. (2022) which uses principal component analysis to only identify lesions as voxels that have an absolute coefficient at about the 20th percentile. Another method, coined principal component functional disconnection (PC-FDC), selects voxels with the most similar time-courses to create the lesion (Pini et al., 2021).

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