Exploratory SEM reveals altered resting-state motor control network connectivity following stroke

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Introduction

- Previous studies have found that stroke alters the effective connectivity of motor execution networks (James, Lu, VanMeter, et al., 2009).
- Here we examined the intrinsic effective connectivity of top-down motor control in stroke survivors relative to healthy participants.
- Stroke survivors with heterogeneous stroke location (8 males) demonstrated moderate deficits in upper limb motor function.
- The relationship between these observed deficits in motor function and intrinsic effective connectivity between brain regions involved in motor control and motor execution were investigated with structural equation modeling (SEM) of resting-state fMRI data (rs-fMRI)

Background

- Stroke is now the leading cause of severe, long-term disability in the United States (Rosamond, Flegal, Friday, et al, 2007).
- Functional neuroimaging has improved stroke research by identifying the neuroanatomic components of the human motor system and elucidating the complex, dynamic neural interactions underlying task-related motor function (Cabeza and Nyberg, 2000).
- rs-fMRI of the motor network circumvents the confounds introduced by task difficulty.

Research Goals

- To evaluate rs-fMRI connectivity of motor circuits in the brain of healthy individuals through exploratory SEM.
- To characterize any potential alterations in rs-fMRI between motor control and execution circuits in stroke survivors based on an exploratory model of healthy controls.

Hypotheses

- We propose that stroke survivors' data will differ significantly from an exploratory SEM derived from able-bodied participants' data. Specifically, in connectivity from motor control (fronto-parietal) to motor execution circuits (primary motor).
- Furthermore, differences between the healthy control and stroke survivor models will reflect how stroke affects motor network connectivity.

Methods

Participants

- **15 stroke surviviors** (8 male) who had sustained a single stroke with **upper extremity hemiparesis**
- **6 patients** had **left** hemiparesis
- **7 patients** had **right** hemiparesis
- **12 able-bodied** volunteers (5 males; Controls)

Data Analyses

Acquisition

- **rs-fMRI**: *130 time points (~5 min each)*

Pre-Processing

- **SPM5**; **slice-timing**, **band-pass** filter, **motion-corrected**, **realigned**, and **unwarped**.
- Unified Segmentation **Normalization**
- **Smoothing** at FWHM= 6 x 6 x 6 mm

ROI Definition

- Defined using a **mixed seed-based** and **data-driven correlation** mapping procedure
- Primary motor cortex **(M1)** and superior parietal **(PAR)** were selected as seeds.
- **M1 seed** was identified by "**hand knob**" anatomic landmark (James et al., 2009).
- **M1 seed map** guided the **subject-wise** placement of 4 additional **6-mm** ROIs:
  - Bilateral primary motor cortex **(M1)**
  - Bilateral dorsal lateral premotor cortex **(pMC)**
  - supplementary motor area **(SMA)**
- **PAR seed** defined using the WFU PickAtlas (Maldjian, Laurienti, et al., 2003) according to AAL coordinates.
- **PAR seed map** guided the **subject-wise** placement of 4 additional **10-mm** ROIs:
  - Bilateral superior parietal **(PAR)**
  - Bilateral inferior frontal **(IF)**

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Contact: Cory Inman, cinman@emory.edu for a color PDF or more info.

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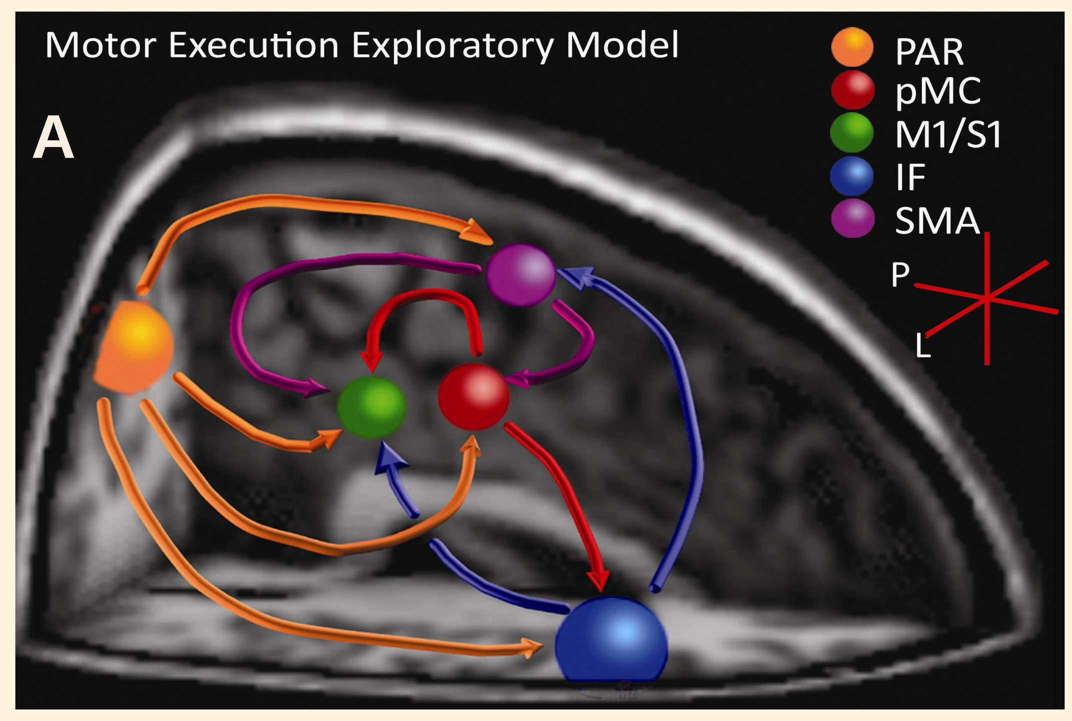
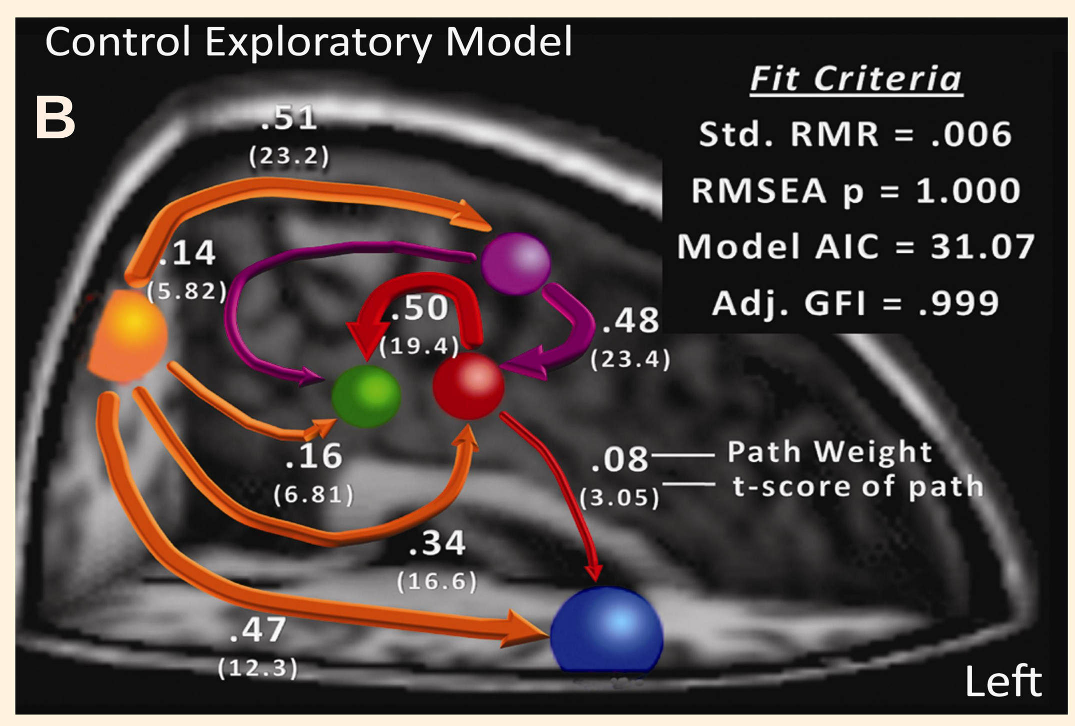
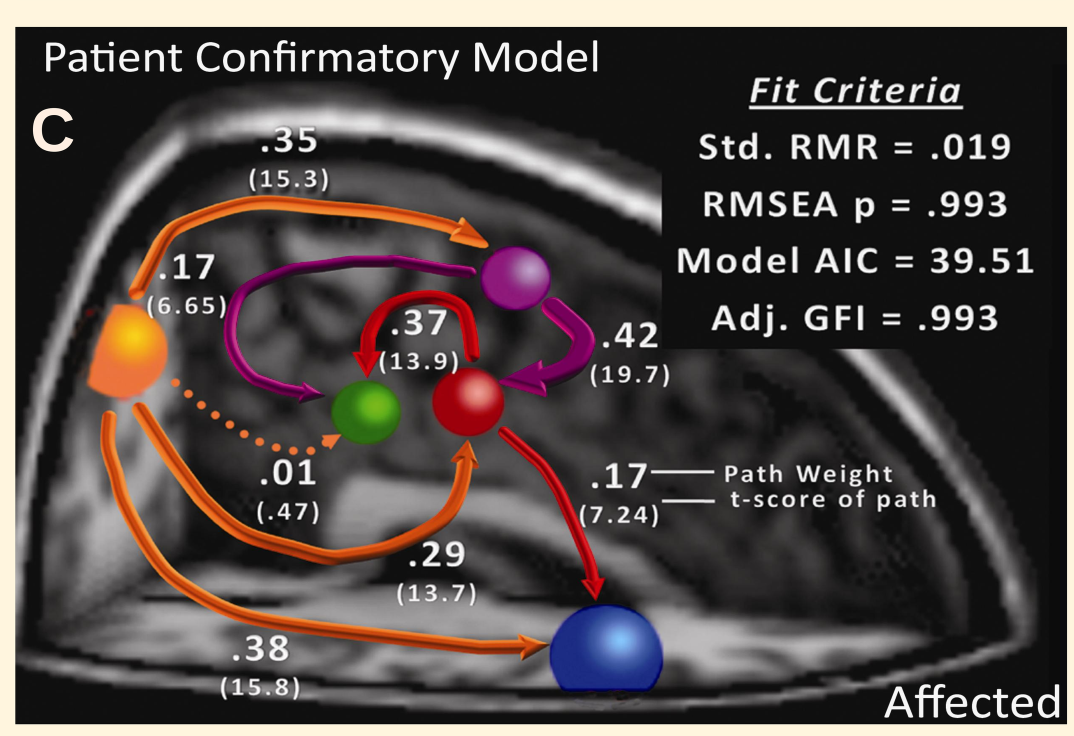
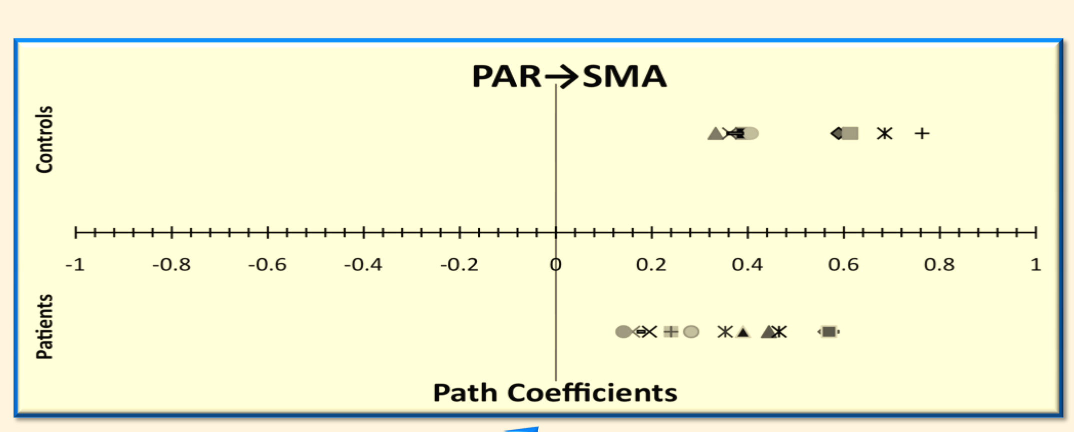
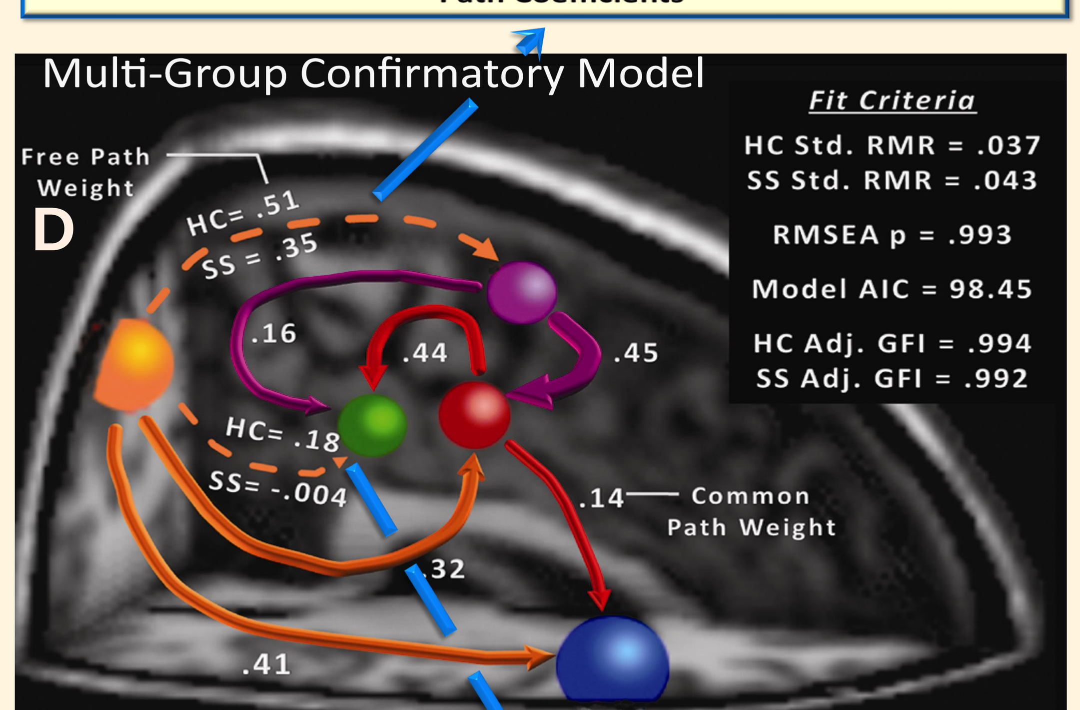
Methods & Results

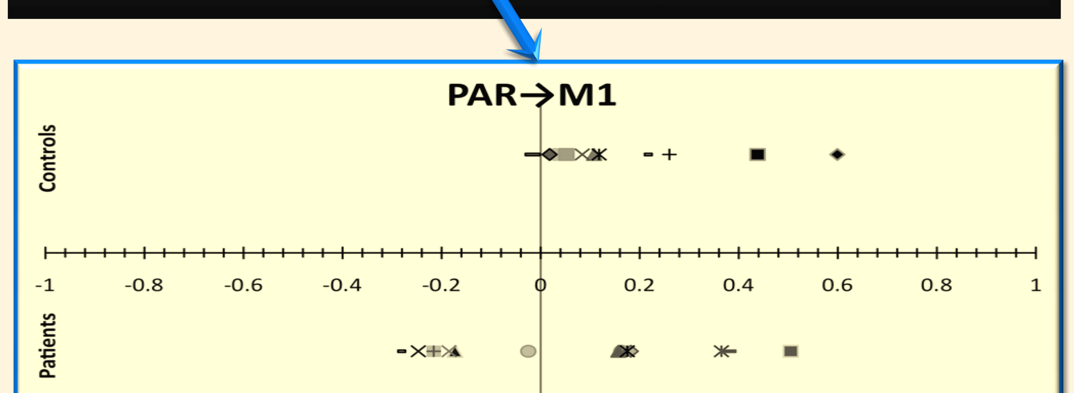












Structural Equation Models

Above each path is the path coefficient for that path. Below each path in parentheses is the t-score for that path. Dotted lines signify non-significant paths or paths that are significantly different between groups.

Structural Equation Modeling

Motor Execution Exploratory Model (A)

- **Exploratory** and **confirmatory SEM** was conducted
- **Path arrows** indicate the **direction of influence**
- **Path coefficients** reflect the **strength of influence** (unit change in SD denoted by β score)
- **Figure A** depicts the model adapted from Solodkin and colleagues (2004) for ***constrained*** **exploratory SEM analysis**.
- Path from **PAR to IF added**

Control Exploratory Model (B)

- **Constrained** model run with the **control group data** using our **exploratory SEM** approach
- The **exploratory model for controls (fig. B)** yielded a similar model to the **motor execution model** from Solodkin et al. (2004).
- **fronto-parietal circuit** influences **all** of the seeded **primary motor areas**
- **Reliability** of the **control exploratory** model was assessed using a **leave-one out methodology**

Patient Confirmatory Model (C)

- Application of the **healthy control model (fig. B) to the patient group dataset (fig. C)** revealed **differences**
- **PAR→M1** path did **not** survive to fit in the model
- Other paths produced **weaker** path weights than the healthy control model
- **None** of the **diminished** path weights **correlated** with individual **upper limb motor function scores** (Fugl-Meyer)
- **Stroke survivor confirmatory model** exhibited an **overall weaker** model with **good fit**

Individual Variability: PAR→SMA

- Histogram of individual subjects' path weights for PAR→SMA.
- Note the difference between the magnitude and mean of control and patient distributions.

Multi-group confirmatory model (D)

- Paths **constrained** to a **constant** value for **both** groups and **then iteratively freed** until the model **statistically fits** both groups
- **All** paths **fixed between** groups, the model did **not significantly fit** either group
- **First path freed** was **PAR→.** Multi-group model **approach** a better fit.
- The **next** path freed was **PAR→SMA**. Resulting model had a **good** fit with both data sets.
- Multi-group model that **best** fit had all paths being held static **except for PAR→M1 and PAR→SMA.**

Individual Variability: PAR→M1

- Histogram of individual subjects' pathweights for PAR→M1.
- Note the relatively normal distribution in the controls, while the distribution for the patients is quite variable and multi-modal.
- Indiv. Path weights did not predict motor function.

Discussion

- SEMs derived from **data-driven analyses** demonstrated that **top-down connections** of **motor guidance systems** to the rs-fMRI **motor network** are **disrupted** in stroke survivors, namely:
  - **PAR→M1 & PAR→SMA**

Implications

- **Motor control deficits** following stroke may **stem** from **disconnect** between **motor guidance systems** and the **primary motor network**
- **Fronto-parietal inputs into primary motor regions guide** motor intentions, decision-making, trajectories of movement, and coordination of multiple body parts (Andersen and Cui, 2009).
- **Multi-group** shows **top-down connections** are **critical** for **normal** functioning and are **damaged** in **stroke survivors** with **impaired upper extremity control**.
- **Stroke survivor** model **distinct** from both the **execution model** and **healthy exploratory model**
- **Variability of PAR to M1** path weights **across patients** makes the **PAR's** influence on **M1 negligible** in **stroke survivor confirmatory model**
- Similar to our findings**, James et al. (2009)** found **altered** rs-fMRI primary motor connectivity in stroke survivors through **exploratory SEM after rehab**
  - i.e.; **Bilateral motor network plasticity** from **affected** to **unaffected regions** and visa versa
- Characterizing **resting-state networks in stroke** informs **rehabilitation therapists** of **cognitive mechanisms** that **need therapeutic attention following stroke.**