

Longitudinal Changes in Microstructure and Function in the Frontoparietal Network in an Older Cohort

Marlon Gonzales,¹ Panpan Zhang,^{2,3,4} Dandan Liu,^{2,3,4} Kimberly R. Pechman,^{2,3} Niranjana Shashikumar,^{2,3} Yukti Vyas,^{2,3} , Bennett A. Landman,^{2,3,5,6,7}
Derek B. Archer,^{2,3,8} Timothy J. Hohman,^{2,3,8} Angela L. Jefferson,^{2,3,8,9} Sarah E. Goodale^{2,3}

Vanderbilt Memory
& Alzheimer's Center

VANDERBILT UNIVERSITY
MEDICAL CENTER

¹School of Medicine, Meharry Medical College, Nashville, TN, USA; ²Vanderbilt Memory and Alzheimer's Center, Vanderbilt University School of Medicine, Nashville, TN, USA; ³Vanderbilt Alzheimer's Disease Research Center, Nashville, TN, USA; ⁴Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA; ⁵Department of Electrical and Computer Engineering, Vanderbilt University, Nashville, TN, USA; ⁶Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, USA; ⁷Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA; ⁸Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA; ⁹Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

VANDERBILT MEMORY & ALZHEIMER'S CENTER

Background

- Brain structure and function decline in aging and are associated with cognitive decline, especially in the frontoparietal network (FPN).
- Some brain regions have increased functional activity that may be a compensatory neural change to maintain cognitive performance.
- The goal of this study was to leverage the Vanderbilt Memory and Aging Project's (VMAP's) longitudinal dataset to investigate diffusion and functional biomarkers of the FPN longitudinally in a cognitively unimpaired older adults to determine early drivers of age-related change.

Methods

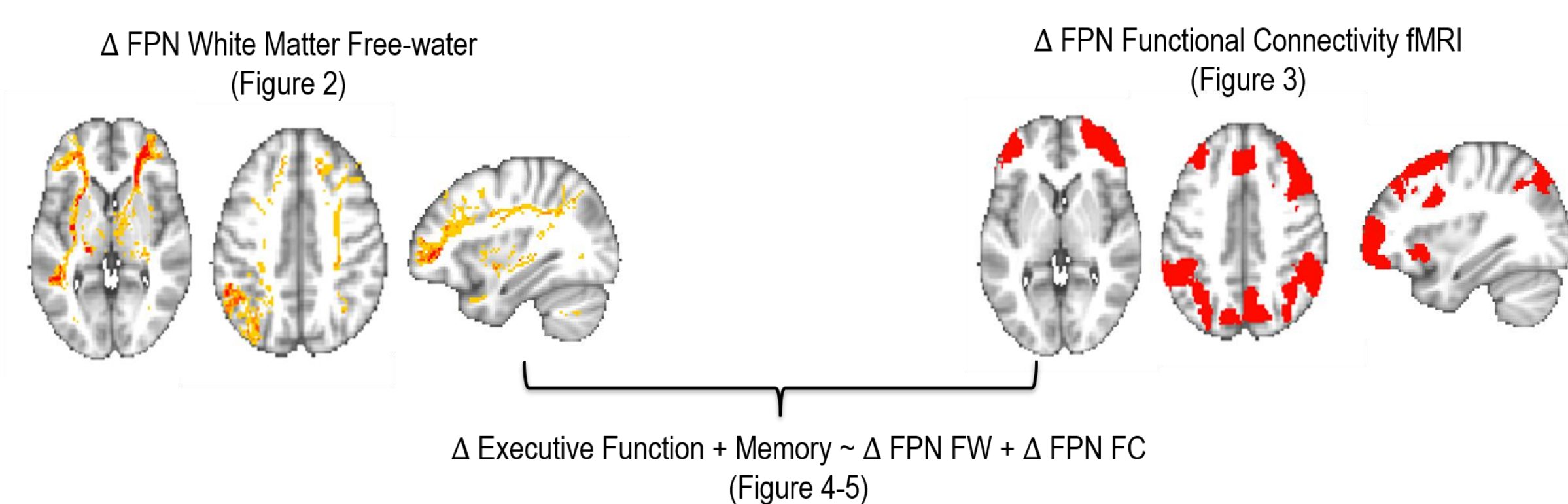
- A subset of the VMAP participants (n=96; age 70.0±6.4 years; 68% male) underwent longitudinal 3T structural, functional, and diffusion magnetic resonance imaging (MRI) over 6.7±1.8 years (**Table 1**).
- Functional MRI data (377 scans) underwent standard preprocessing. Functional connectivity (FC) was calculated using the Schaefer atlas for within-FPN and FPN-to-whole-brain connectivity.
- Diffusion MRI data (433 scans) were processed using the PreQual pipeline and used to derive free-water (FW), fractional anisotropy (FA), axial diffusivity (AD), medial diffusivity (MD), and radial diffusivity (RD) from 20 FPN white matter tracts.
- Linear mixed-effects models assessed (1) age- and time-related changes in FC and diffusion metrics and (2) whether longitudinal changes in these measures were associated with changes in executive function and memory (**Figure 1**). Models were adjusted for sex, race, *APOE*-ε4 status, diagnosis, scanner effects, and Framingham Stroke Risk Profile minus age points.

Table 1. Participant Characteristics

Characteristic	Combined (n = 96)
Age, years	70.0±6.4
Education, years	16.3±2.5
Sex, % Female	32%
Race, % non-Hispanic White	88%
FSRP score*	5.85±2.92
<i>APOE</i> -ε4, % carrier	32%
Mean Scan Span, years	6.68±1.78
Mean Number of scanned epochs	4.51±0.833
Cognitive diagnosis, % Normal	73%
Cognitive diagnosis, % Ambiguous At Risk	7%
Cognitive diagnosis, %MCI	20%

Note. Values are denoted as mean±standard deviation or frequency. *APOE*=apolipoprotein E gene; FSRP=Framingham Stroke Risk Profile; MCI=mild cognitive impairment. *A modified FSRP score excluded points assigned to age.

Figure 1. Flow Chart for Structure-Function and Cognition



Results

- Age significantly influenced longitudinal changes in 20 FPN white matter tracts and 13 within-network FPN FC regions after FDR correction (**Figures 2 and 3**).
- FW increased across frontal and parietal pathways, suggesting progressive extracellular water accumulation and microstructural vulnerability within the FPN.
- FA, MD, AD, and RD demonstrated significant longitudinal changes, indicating progressive alterations in FPN related white matter microstructure with aging.
- Within-FPN FC increased over time. There were no across-brain FPN FC regions remained significant after FDR correction.
- Increased FW and RD were associated with faster memory and executive function decline, respectively, while increased FA was associated with improved executive performance (**Figure 4**).
- No significant associations were observed between FC and longitudinal cognitive decline (p>0.05).

Figure 2. Rate of Change in FPN Diffusion Metrics

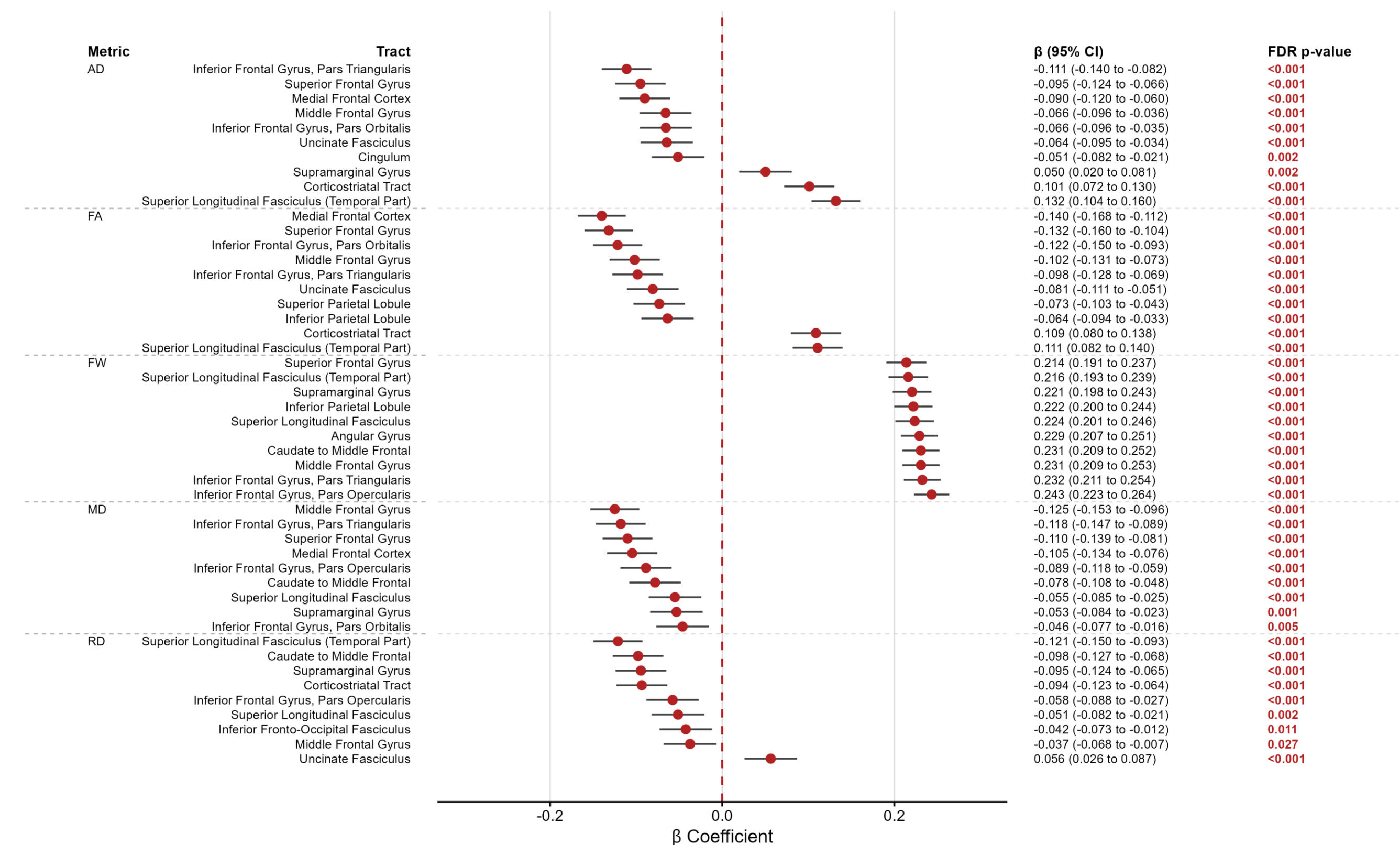


Figure 3. Rate of Change in Within-FPN Connectivity

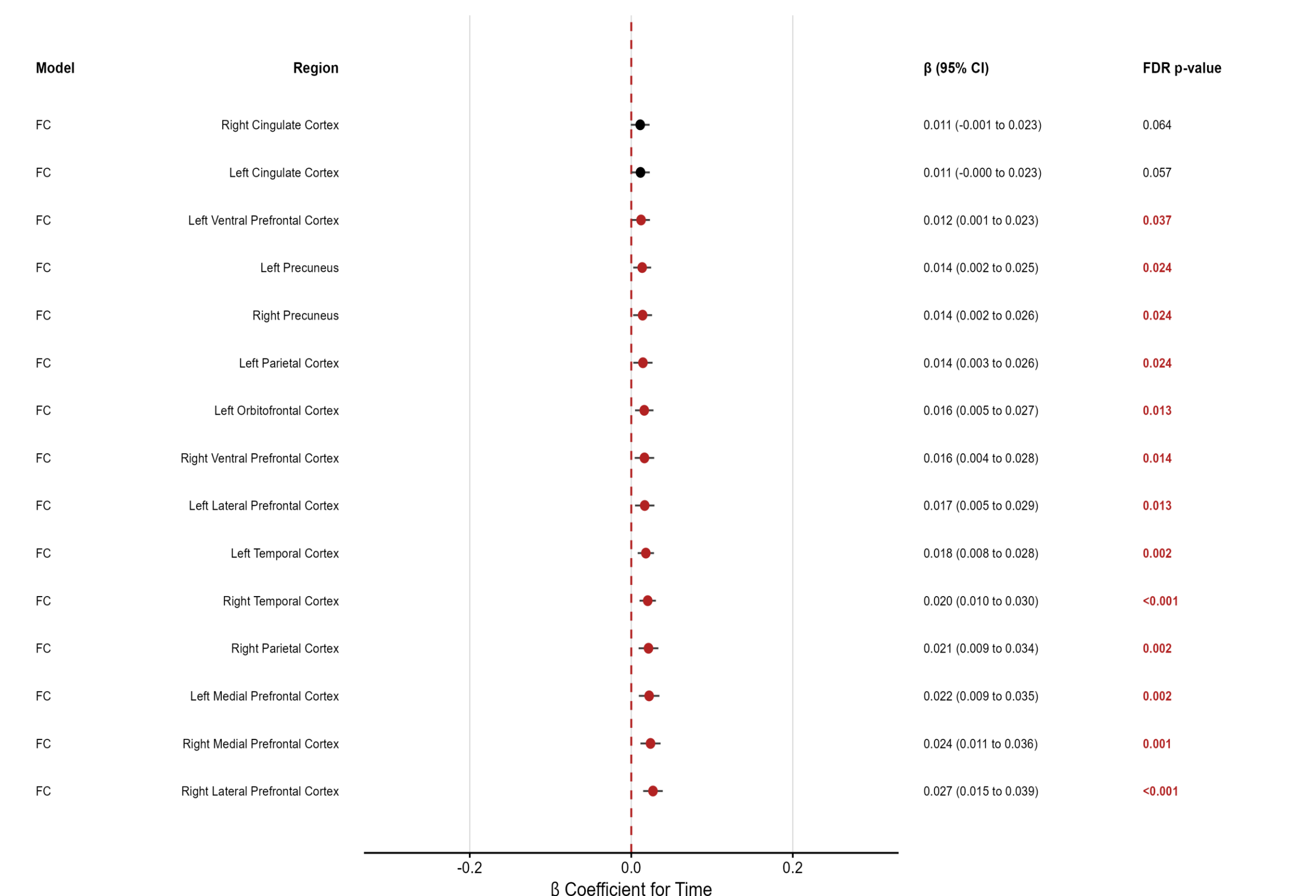
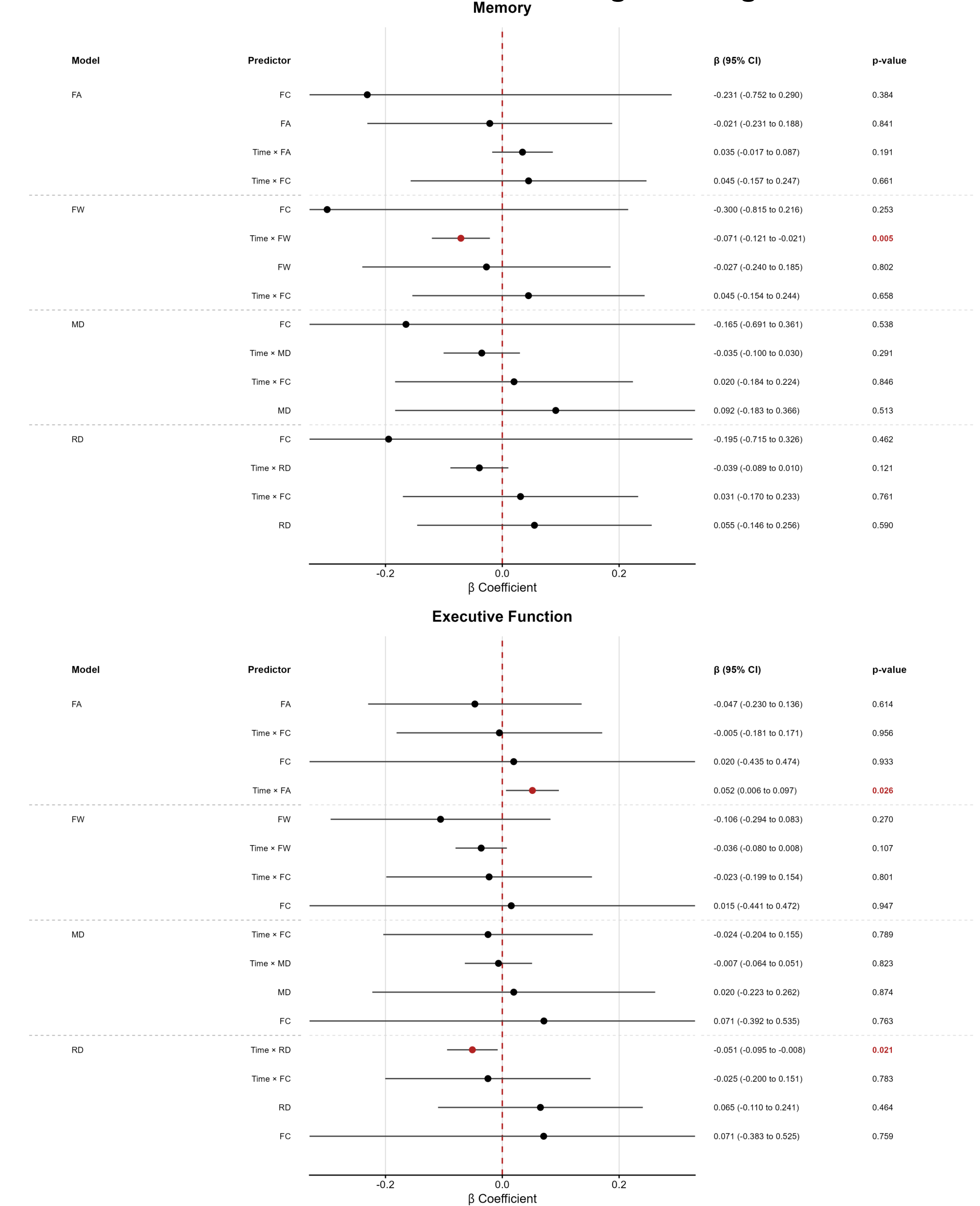


Figure 4. Longitudinal effects of Within-FPN Connectivity and FPN Diffusion Metrics on Rate of Change in Cognition



Conclusions

- Aging was associated with structural and functional changes over a 6-year period within the FPN, characterized by increased FW, alterations in FA, MD, AD, and RD, and increased within-network FC.
- Increased within-network FC may reflect compensatory network reorganization in response to age-related microstructural vulnerability.
- The absence of significant across-network FC changes suggests that early functional alterations are network-specific rather than globally distributed.
- Longitudinal diffusion MRI changes, particularly FW, FA, and RD, were associated with rates of memory and executive function changes, whereas FC changes were not significantly associated with cognitive trajectories in this cognitively unimpaired cohort.
- These findings support the FPN as a vulnerable network in aging and suggest that diffusion MRI metrics may serve as candidate early imaging markers of cognitive vulnerability and AD-related neurodegenerative processes.