Enhanced brain structure–function coupling in the frontoparietal control network of chronic tobacco smokers

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ABSTRACT

Purpose: This cross-sectional study quantified structural–functional (SC-FC) coupling in chronic tobacco smokers versus non-smokers using multimodal MR imaging, testing whether smoking is associated with altered correspondence between white-matter architecture and resting-state functional connectivity..

Methods: A total of 102 participants (51 smokers, 51 non-smokers) were recruited for the study and underwent brain scans on a whole-body 3T MRI system. Structural connectivity (SC) matrices were derived from MRtrix3 tractography with SIFT2 weighting and volume correction, and functional connectivity (FC) matrices were constructed. SC–FC coupling, corrected for inter-regional distance, was quantified for the whole brain and the seven Schaefer–Yeo canonical networks using Spearman correlations, averaged across network densities 10-30% to reduce bias from single-thresholding selection in sparse brain networks. Group differences were tested using clusterwise non-parametric permutation (n = 5000) analysis with family-wise error (FWE) correction.

Results: Smokers were older than non-smokers (48±12 vs. 41±13 years, p = 0.007), with no sex differences between groups. Smokers showed higher SC-FC coupling within the Control/frontoparietal control network (FPCN) compared to controls. Statistical significance was observed at 22-30% (FWE-corrected, p<0.05) thresholds with age, sex, and education level as covariates. No significant differences were found for the other networks or subcortical structures.

Conclusions: Enhanced SC-FC coupling in the FPCN of smokers indicates a closer alignment between executive-control white matter pathways and intrinsic functional dynamics. This pattern may reflect reduced neural flexibility, where attention and control processes become more rigidly shaped by underlying white-matter pathways. Such rigidity could help explain the habitual, cue-driven patterns of control often observed in tobacco addiction.

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INTRODUCTION

Tobacco smoking remains a leading preventable cause of disease and is associated with widespread changes in brain structure and function. Chronic nicotine exposure alters networks involved in reward, attention, and cognitive control, with prior studies showing structural deficits and disrupted functional connectivity. However, these domains are typically examined separately, leaving unclear whether functional alterations reflect underlying structural damage or network reorganization.

Structural-functional (SC-FC) coupling links white-matter architecture with functional connectivity, providing a systems-level measure of brain organization. While altered coupling has been observed in other clinical conditions, it has not been studied in smokers.

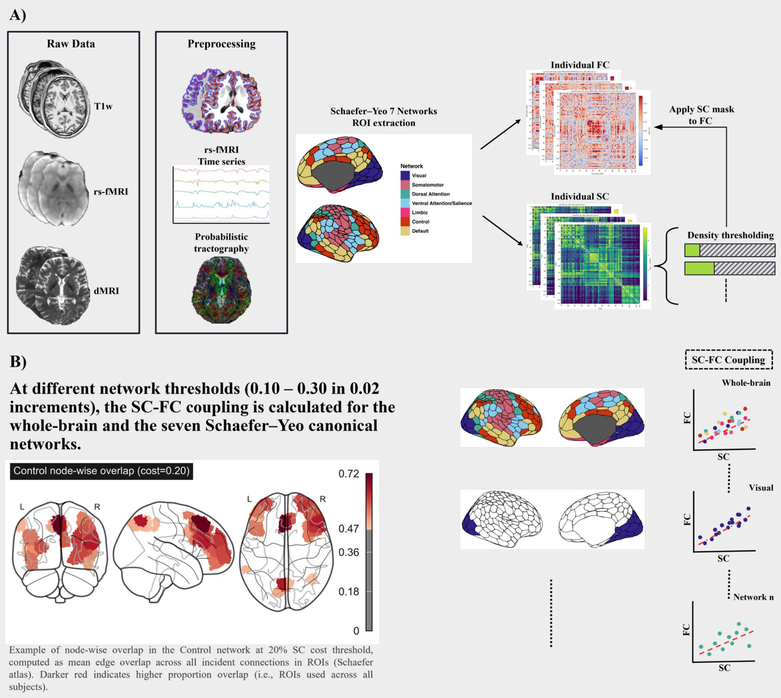
Here, we quantify SC-FC coupling in chronic smokers and non-smokers using multimodal MRI to assess whether smoking is associated with altered structure–function relationships across brain networks

METHODS AND MATERIALS

A total of 102 participants (51 smokers, 51 non-smokers) were recruited and scanned on a whole-body 3T MRI system. Functional MRI data were preprocessed with *fMRIPrep*[1], and diffusion MRI data were processed with *QSIPrep*[2] and *QSIRecon*[2] using standardized MRtrix3-based workflows for reconstruction and tractography.

FC and SC matrices were constructed using the Schaefer atlas[3] (n = 100-400; Yeo 7 networks). FC was calculated from denoised, band-pass filtered BOLD time series after scrubbing volumes with framewise displacement > 0.5 mm, and SC was derived from diffusion MRI using whole-brain tractography, multi-tissue CSD, and SIFT2-weighted, volume-normalized streamline counts.

SC–FC coupling was defined as the Spearman correlation between SC and FC edge weights, computed globally and within canonical networks excluding the cerebellum. SC matrices were proportionally thresholded across 10–30% densities, with matched FC edges and distance effects regressed out.



Example of node-wise overlap in the Control network at 20% SC cost threshold, computed as mean edge overlap across all incident connections in ROIs (Schaefer atlas). Darker red indicates higher proportion overlap (i.e., ROIs used across all subjects).

Figure 1. Overview of study procedures: **A)** Preprocessing of raw data and construction of individual FC and SC matrices, **B)** SC-FC coupling calculation at different network density thresholds for the whole-brain, the 7 Schaefer-Yeo Canonical networks, and subcortical structures.

RESULTS

- Smokers showed higher SC-FC coupling in the frontoparietal control network (FPCN) than non-smokers, with the most consistent differences observed across mid-to-higher within-network densities and across atlas resolutions after adjusting for age, sex, and education (**Figure 2**).
- The effect remained directionally similar in sensitivity models that also included motion and global signal.

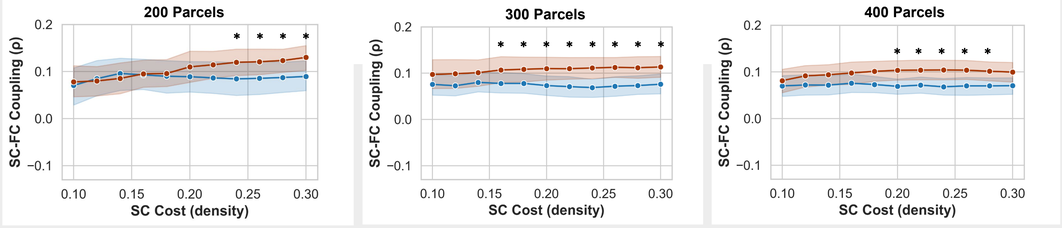


Figure 2. Increased SC–FC coupling in the FPCN in smokers versus non-smokers across parcellation resolutions and SC density thresholds. Mean SC–FC coupling (ρ) is plotted across within-network SC cost (density) for 200 – 400 parcel atlases; red lines = smokers, blue lines = non-, shaded areas = 95% confidence interval. * = density levels where the smoker > non-smoker difference reached statistical significance after adjusting for age, sex, and education; sensitivity models including motion and global signal produced directionally similar results.

- Next, we mapped node-wise SC-FC coupling within the FPCN to show the spatial distribution of coupling strength in smokers and non-smokers. See **Figure 3** for example at 300 parcels.

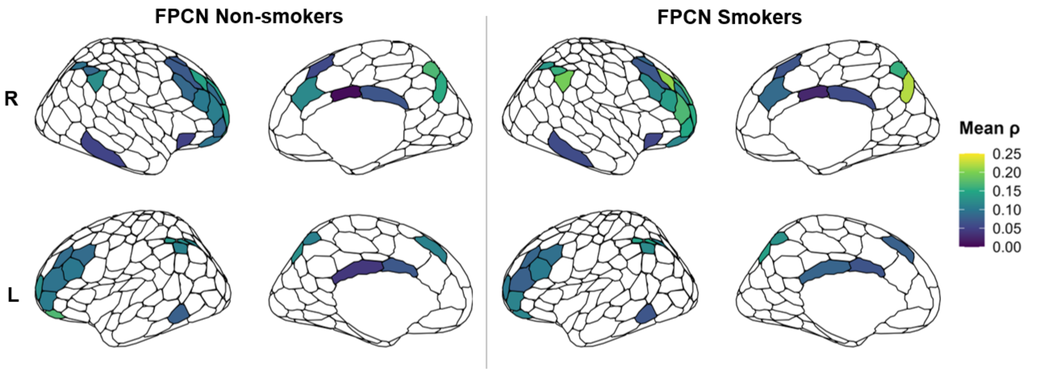


Figure 3. Group-averaged node-wise SC-FC coupling within the FPCN) Maps show the spatial distribution of mean SC-FC coupling (ρ) for non-smokers and smokers, averaged within each group across FPCN nodes. Warmer colors indicate higher coupling and cooler colors indicate lower coupling, with the color bar showing mean ρ values. Left- and right-hemisphere views are shown for both lateral and medial surfaces.

DISCUSSION AND CONCLUSION

Discussion: Chronic smoking was associated with higher SC-FC coupling in the frontoparietal control network (FPCN), suggesting altered structure–function correspondence in executive-control circuitry. Because the FPCN is typically considered a flexible control system, this elevated coupling may reflect reduced flexibility, compensatory reliance on structural pathways, or a premorbid trait related to vulnerability to smoking.

The absence of associations with smoking severity argues against a simple dose-response effect and suggests that this may reflect a more stable network-level feature. Overall, the findings are hypothesis-generating and point to altered FPCN organization in chronic smoking.

Conclusion:

- Smokers showed higher SC-FC coupling in the FPCN than non-smokers.
- The effect was specific to executive-control circuitry.
- No clear relationship with smoking severity was observed.
- Elevated coupling may reflect reduced flexibility, compensation, or a premorbid trait.

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