

Functional Connectivity of striatal subregions as a function of chronic cigarette smoking and acute nicotine administration

R. Poudel¹, M. J. Tobia², M. C. Riedel², A. R. Laird², T. J. Ross³, B. J. Salmeron³, E. A. Stein³, M. T. Sutherland¹

¹ Department of Psychology, Florida International University, Miami, FL

² Department of Physics, Florida International University, Miami, FL

³ Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, NIH/DHHS, Baltimore, MD

Introduction

The striatum and its interconnected circuitry are critically involved in drug-seeking and -taking behaviors, yet little is understood about the striatum's circuit-level interactions with other brain regions linked with chronic cigarette smoking and acute nicotine administration^{1,2}. Utilizing resting-state functional connectivity (rsFC) assessments, we characterized alterations in striatum-centered circuitry as a function of a chronic smoking history (i.e., abstinent smokers versus nonsmokers) and acute pharmacological administration (i.e., nicotine and varenicline). Regarding regional rsFC patterns, we expected to replicate results from a striatal rsFC study³. Considering group effects (smokers vs. nonsmokers), we expected to observe altered rsFC among smokers between striatum and reward-related regions such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)³. Regarding drug effects, we expected to see alteration in rsFC of the striatum with brain regions including OFC and insula^{4,5}. Further, we examined brain-behavior relationship by correlating the rsFC values associated with brain regions showing significant group and drug effects with smoking behavior and behavioral performance in a task, respectively.

Methods

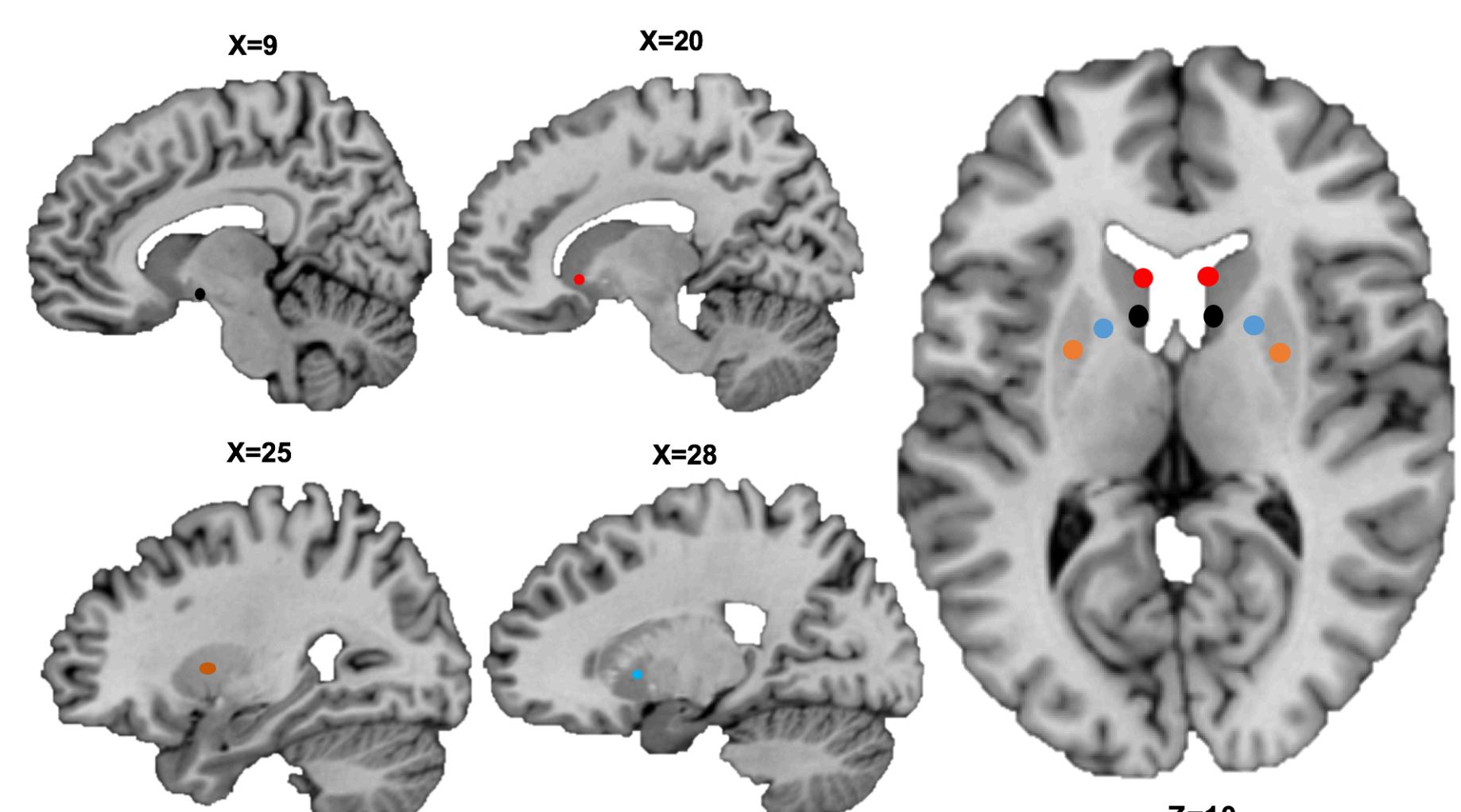
Participants. Non-treatment seeking smokers ($n=24$; ≥ 10 cigs/day for > 2 years) and non-smoking controls ($n=20$). Carbon monoxide (CO) levels confirmed overnight abstinence.

Drug manipulations. Scanned at 6 time points in a two-drug, placebo-controlled pharmacological administration study.

- Drug conditions were counter-balanced across participants.
 - 3 varenicline pill conditions (PILL factor: pre-pill vs. varenicline vs. placebo).
 - 2 transdermal nicotine patch conditions (PATCH factor: nicotine vs. placebo).

fMRI data collection. 8 minutes eyes closed resting scan (2.5-3 hrs after patch application).

Striatal seed regions. A total of 8 seeds were utilized³: [1] (Ventral striatum inferior, **Vsi**: $x = \pm 9$, $y = 9$, $z = -8$), [2] (Dorsal Caudate, **DC**: $x = \pm 13$, $y = 15$, $z = 9$), [3] (Dorsal Caudal Putamen, **DCP**: $x = \pm 28$, $y = 1$, $z = 3$), [4] (Ventral Rostral Putamen, **VRP**: $x = \pm 20$, $y = 12$, $z = -3$).



rsFC preprocessing and analysis. Conducted in AFNI⁶: alignment, motion censoring, registration, smoothing, seed time series extraction, seed based functional connectivity analysis.

Regional effects. To characterize rsFC patterns for each seed region, one-sample t-tests were conducted (AFNI's 3dttest++: $P_{\text{corrected}} = 0.05$, $P_{\text{voxelwise}} = 0.001$, cluster extent: 35).

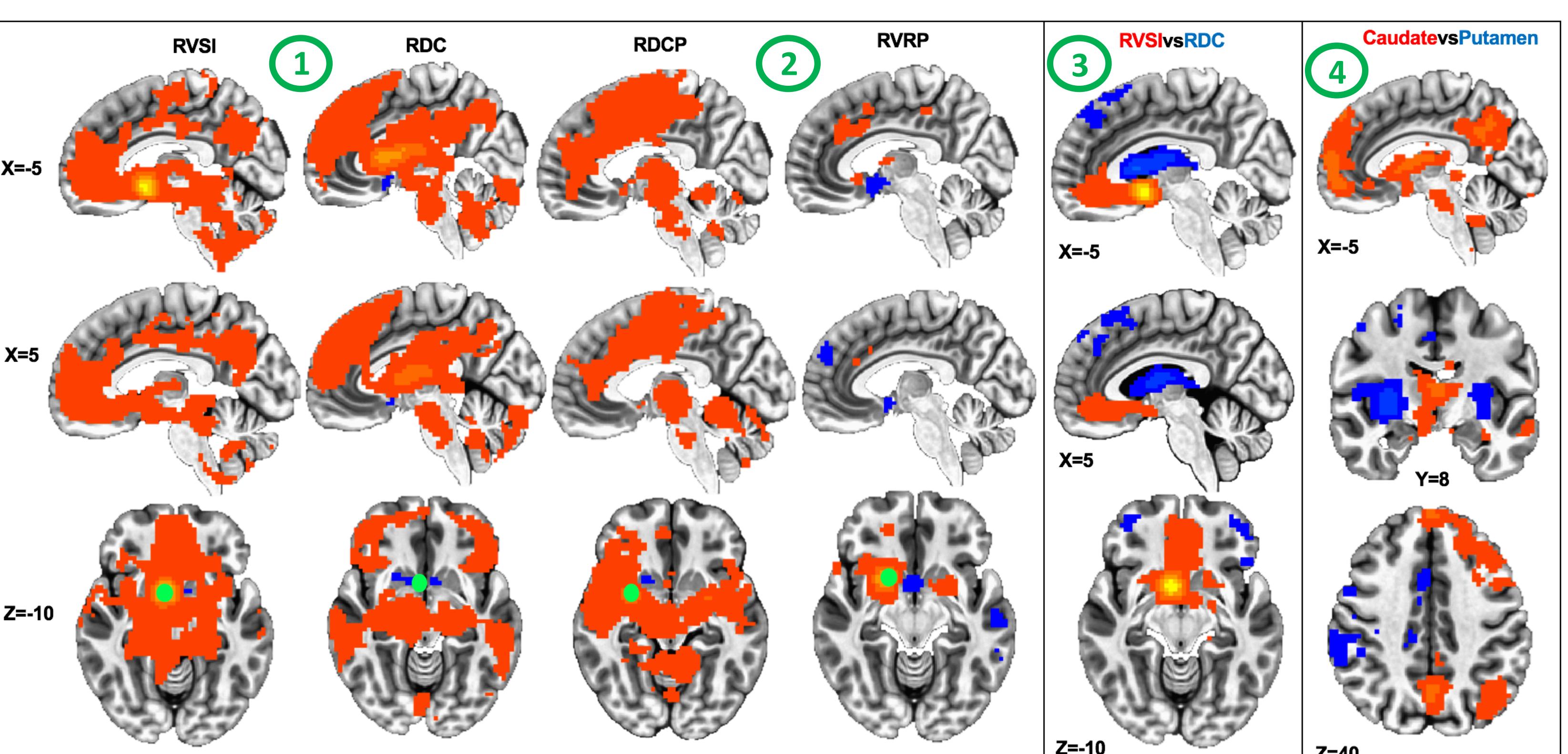
Group effects. To delineate differential rsFC patterns between smokers vs. nonsmokers, independent-samples t-tests were conducted (AFNI's 3dttest++: $P_{\text{corrected}} = 0.05$, $P_{\text{voxelwise}} = 0.001$, cluster extent: 35). The rsFC values from clusters showing group differences were tested for correlation with Fagerstrom Test for Nicotine Dependence (FTND) scores and pack years.

Drug effects. To elucidate the impact of acute drug manipulations, whole brain 3X2X2 linear mixed effects models were employed (AFNI's 3dLME: $P_{\text{corrected}} = 0.05$, $P_{\text{voxelwise}} = 0.001$, cluster extent: 35). The rsFC values from clusters showing drug effects were tested for correlation with positive affect and behavioral performance in a task (% no-response and reaction time).

Results

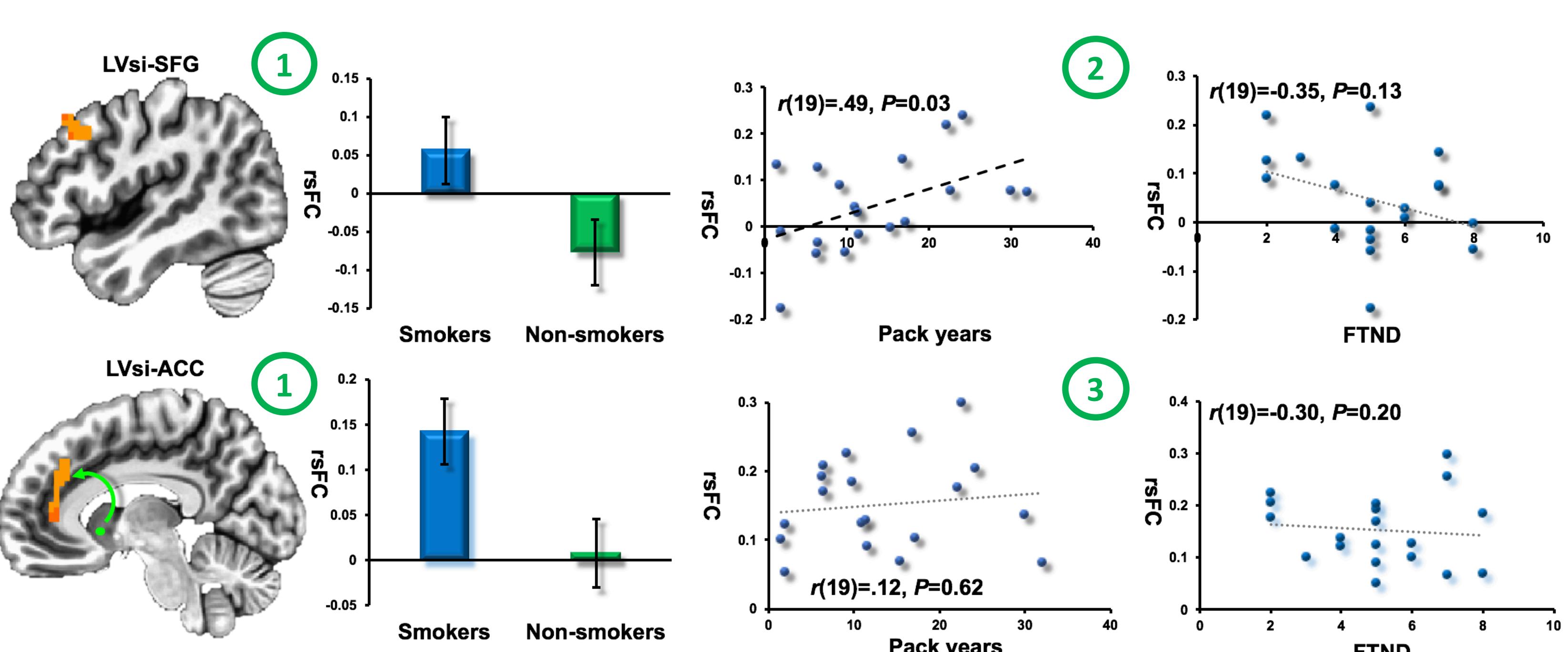
A) Regional Effects.

- As expected, ventral striatal seeds (RVsi and RDC) were functionally coupled with frontal, cingulate, and parietal regions.
- Dorsal striatal seeds (RDCP and RVRP) were functionally connected with sensorimotor regions.
- Direct statistical comparison of Vsi and DC showed increased rsFC of Vsi seed with OFC and DC seed with superior frontal cortex.
- Caudate was functionally connected with reward-related regions compared to putamen which was coupled with sensorimotor regions.



B) Group Effects.

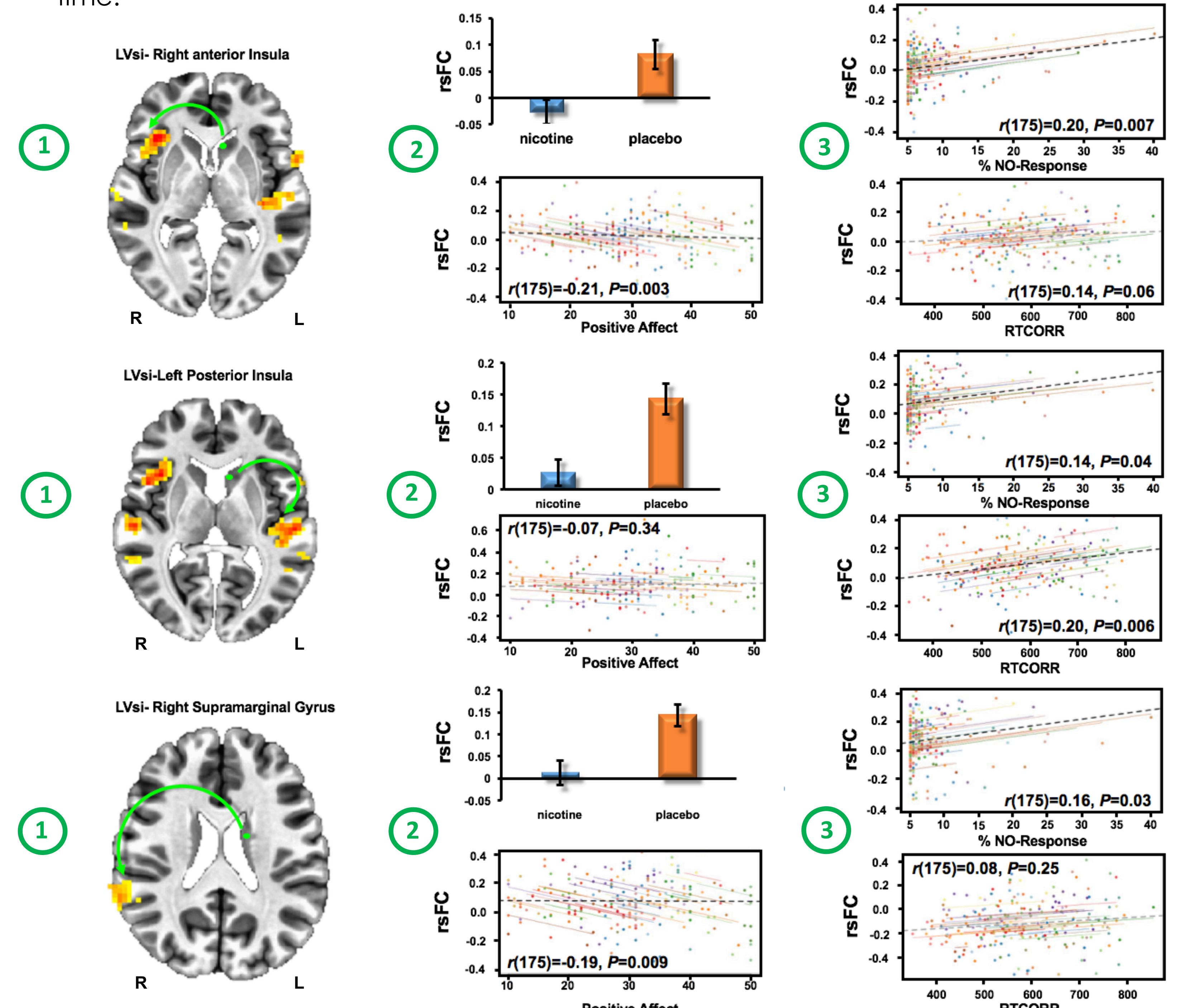
- Abstinent smokers (vs. nonsmokers) showed greater coupling of LVsi seed with superior frontal gyrus (SFG) and ACC.
- Among smokers, rsFC values in the LVsi-SFG circuit was positively correlated with pack years [$r(19) = 0.49$, $P = 0.03$] but not with FTND scores [$r(19) = -0.35$, $P = .13$].
- Among smokers, rsFC values in the LVsi-ACC circuit was not correlated with either pack years [$r(19) = 0.12$, $P = .62$] or FTND scores [$r(19) = -0.30$, $P = .20$].



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C) Drug Effects.

- A main effect of PATCH was observed in the following circuits: LVsi-right anterior insula (rAI), LVsi-left posterior insula (lPI), LVsi-right supramarginal gyrus (rSG), [LVsi-inferior frontal gyrus and LVsi-bilateral superior temporal gyrus (not shown in the figure below)].
- Specifically, a nicotine-induced decrease in the rsFC was observed in these specific circuits. Further, LVsi-rAI and LVsi-rSG rsFC values were significantly correlated with affect.
- Similarly, the rsFC values in the LVsi-rAI and LVsi-rSG circuits were significantly correlated with reduced behavioral performance in a subsequent task (% no-response), and rsFC values in the LVsi-lPI circuit was significantly correlated with % no-response and reaction time.



Conclusions

- These results largely replicated rsFC patterns of 8 striatal seeds from a previous study³.
 - A chronic smoking history was associated with increased rsFC in LVsi-ACC and LVsi-SFG circuits, and the rsFC in LVsi-SFG circuit was related to lifetime exposure to nicotine.
 - Acute nicotine administration reduced rsFC in a LVsi-insula and LVsi-rSG circuits which was related to self-reported mood and behavioral performance in a subsequent task.
- These results indicate a dissociation between the effects of chronic nicotine dependence (smokers vs. nonsmokers) and acute nicotine administration (nicotine vs. placebo) on rsFC of striatal subregions.

References:

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