Nicotine and Tobacco Research, 2024, **26**, 1305–1312
https://doi.org/10.1093/ntr/ntae084
Advance access publication 16 April 2024
Original Investigation

Smoking Progression and Nicotine-Enhanced Reward Sensitivity Predicted by Resting-State Functional Connectivity in Salience and Executive Control Networks

Matthew P. Gunn MA[1], Gregory M. Rose PhD[2], Alexis E. Whitton PhD[3,4], Diego A. Pizzagalli PhD[3], David G. Gilbert PhD[1]

[1]Department of Psychology, Southern Illinois University, Carbondale, IL, USA
[2]Department of Anatomy, Southern Illinois University School of Medicine, Carbondale, IL, USA
[3]Division of Medical Science, McLean Hospital & Harvard Medical School, Boston, MA, USA
[4]Black Dog Institute, University of New South Wales, Sydney, NSW, Australia

Corresponding Author: Matthew P. Gunn, MA, Southern Illinois University, Mail Code 6502, Carbondale, Illinois, 62901-6502, USA. Telephone: 217-652-7701; E-mail: matthewpgunn@gmail.com

Abstract

Introduction: The neural underpinnings underlying individual differences in nicotine-enhanced reward sensitivity (NERS) and smoking progression are poorly understood. Thus, we investigated whether brain resting-state functional connectivity (rsFC.) during smoking abstinence predicts NERS and smoking progression in young light smokers. We hypothesized that high rsFC between brain areas with high densities of nicotinic receptors (insula, anterior cingulate cortex [ACC], hippocampus, thalamus) and areas involved in reward-seeking (nucleus accumbens [NAcc], prefrontal cortex [PFC]) would predict NERS and smoking progression.

Aims and Methods: Young light smokers ($N = 64$, age 18–24, M = 1.89 cigarettes/day) participated in the study. These individuals smoked between 5 and 35 cigarettes per week and lifetime use never exceeded 35 cigarettes per week. Their rsFC was assessed using functional magnetic resonance imaging after 14 hours of nicotine deprivation. Subjects also completed a probabilistic reward task after smoking a placebo on 1 day and a regular cigarette on another day.

Results: The probabilistic-reward-task assessed greater NERS was associated with greater rsFC between the right anterior PFC and right NAcc, but with reduced rsFC between the ACC and left inferior prefrontal gyrus and the insula and ACC. Decreased rsFC within the salience network (ACC and insula) predicted increased smoking progression across 18 months and greater NERS.

Conclusions: These findings provide the first evidence that differences in rsFCs in young light smokers are associated with nicotine-enhanced reward sensitivity and smoking progression.

Clinical trial registration: NCT02129387 (preregistered hypothesis: www.clinicaltrials.gov).

Implications: Weaker rsFC within the salience network predicted greater NERS and smoking progression. These findings suggest that salience network rsFC and drug-enhanced reward sensitivity may be useful tools and potential endophenotypes for reward sensitivity and drug-dependence research.

Introduction

A large body of evidence supports the view that the rewarding/addictive properties of nicotine (NIC) are due to its ability to reduce negative affect and enhance positive affect, reward response, and executive functioning.[1,2] Many studies using blood oxygenation level-dependent functional magnetic resonance imaging (fMRI) have characterized brain networks underlying the cognitive, affective, and craving-related effects of smoking abstinence, acute nicotine, and smoking-related stimuli.[3–5] However, no studies have used resting-state functional connectivity (FC; rsFC) or other brain functioning indices to predict smoking progression in young light smokers or to assess nicotine-enhanced reward sensitivity (NERS) in this group, despite studies showing relationships of rsFC within and between reward, attention, and emotion-related regions.[6,7] This knowledge deficit related to young light smokers is problematic given that the proportion of light smokers has increased in recent years,[8] especially in younger age groups.[9] Virtually nothing is known about the individual (between subjects) differences in neurobiological and nicotine reinforcement factors that explain why 21%–35% of young light smokers increase to 5 + NIC use per day, while about 27%–32% quit smoking and the rest maintain their baseline smoking rates across 2 years.[10] We hypothesized that smoking progression and NERS could be predicted by individual differences in rsFC between nicotinic cholinergic receptor (nAChRs)-rich brain regions.

Brain regions with high-density nAChRs, including the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insular cortex, amygdala,[11] prefrontal cortex (PFC), hippocampus, nucleus accumbens (NAcc), ventral tegmental areas,[12] and thalamus,[13] are influenced by NIC administration,

Received: August 28, 2023. Revised: March 14, 2024. Accepted: April 8 2024.

smoker status, and smoking withdrawal.[14] In their review, Fedota and Stein (2015) found that rsFC between the insular cortex and other brain regions was altered by smoking abstinence (six of the eight studies), smoker versus nonsmoker status (seven of the twelve studies), and acute nicotine administration (two of the seven studies). Evidence supporting the importance of the insula in smoking motivation is also provided by individual differences in rsFC in the salience network, whose primary hubs include the insula and ACC, which have predicted craving,[15] smoker versus nonsmoker status,[16] and NIC relapse.[17]

Resting-state FC between the regions with a high density of nAChR has been used to predict NIC smoking status,[16] NIC relapse,[7] and NIC addiction severity,[18] indicating the potential of rsFC to provide valuable insights into smoking-related outcomes. Attention enhancement is a primary smoking motivation,[19] and NIC enhances task-assessed attention, especially in individuals with low baseline attentional performance,[20–22] and may contribute to positive affect, smoking progression, and NERS.[23] Thus, individual differences in rsFC might predict between-person differences in the tendency of nicotine to enhance reward sensitivity, a form of attentional enhancement.[24,25] The probabilistic reward task (PRT) has been used to assess the ability of nicotine to enhance responses to rewards.[24–27] The PRT assesses change of positive reinforcement as a function of reward magnitude, likely relying on noradrenergic, serotonergic, and dopaminergic activity, and involves several structures important to NIC addiction.[28] It is known that acute NIC administration, which induces the release of all the above neurotransmitters,[29] promotes PRT-assessed reward sensitivity in rodents and humans.[24–26] Furthermore, PRT performance is impaired during acute NIC abstinence in young light smokers,[27] an effect that can be reversed by NIC administration.

Given the evidence summarized above, we examined whether rsFC in the above-reviewed regions would predict the degree of NERS or smoking progression in individual young light smokers.

Materials and Methods

Participants

Sixty-eight light smokers aged 18–24, taken from a larger study,[27] were used in the current analyses. The inclusion criterion was that the subjects smoked between 5 and 35 cigarettes/week over the past 3 months. Exclusion criteria included weekly psychoactive drug use other than caffeine, consuming greater than 30 alcoholic drinks or more than three uses of marijuana per week, or meeting criteria for or having a history of a mood, anxiety, or psychotic disorder assessed by the Structured Clinical Interview for DSM-IV-TR.[30]Additional exclusion criteria included a history of head injury with loss of consciousness for greater than 10 minutes, current medical or neurological illness, pregnancy, current breastfeeding, and impairment of motor, cognitive or intellectual functioning. Southern Illinois University Human Subjects Committee approved all procedures and subjects gave written informed consent before participating.

Procedure

Participants refrained from smoking for a minimum of 14 hours before each of the three experimental sessions, which was verified by breath carbon monoxide concentrations of <5 ppm. Five minutes before each of the two PRT assessment sessions, individuals smoked either a nicotine or denicotinized placebo cigarette. Participants also abstained from tobacco use for 14 hours before the single subsequent fMRI scanning session. On the day before scanning, individuals completed a session in a mock MRI scanner with scanner noises. No scans were obtained while participants were in a sated state and there were no nonsmoking controls.

Cigarettes

Cigarettes were Camel Lights (RJ Reynolds Tobacco) which delivered 0.8 mg NIC as evaluated by U.S. Federal Trade Commission protocol and Quest 3 (Vector Tobacco) which delivered 0.05 mg NIC (placebo).

Quantified Smoke Delivery System

The quantified smoke delivery system developed by author DGG, produces reliable standard doses of smoke-delivered NIC with a low variation of plasma NIC concentration.[31] This system delivers smoke into the participant's mouth utilizing a motorized syringe. Relative to placebo (ultra-low NIC but normal "tar"), quantified smoke delivery system-delivered nicotine produces the same electroencephalographic, hormonal,[32] mood,[33] and cognitive performance enhancements[19] as ad-lib smoking, yet with lower variability in blood NIC concentration. This allows for improved characterization of individual differences in NIC-related effects.

Probabilistic-Reward Task

The PRT is a well-validated behavioral measure of reward learning used to assess reward sensitivity.[34] During this task, subjects were initially presented with a schematic face consisting of two eyes and a nose, see Figure 1. After an interval of 500 ms, a horizontal line mouth was superimposed on the face for 100 ms. Participants indicated whether the briefly presented mouth was "long" (11 mm) or "short" (10 mm) by pressing a designated key on a response pad. The entire task consisted of 300 trials presented in 100-trial blocks with intervals of 30 seconds between blocks. Forty percent of correctly answered trials resulted in the participants receiving a monetary reward, indicated by the statement, "Correct! You won 20 cents." The long and short mouths were presented at an equal frequency, yet unknown to the subject, were asymmetrically reinforced: one mouth was rewarded three times more frequently (the "rich stimulus") than the other (the "lean stimulus"). Among healthy controls, this asymmetry induces a behavioral response bias toward the rich stimulus and reflects an individual's sensitivity to reward.[34] In a counterbalanced order, two task versions were used to avoid practice effects, with one version consisting of varied mouth length and the other with varied nose length ("long" [11 mm] or "short" [10 mm]). The PRT was initiated approximately 5 minutes after administering nicotine or placebo. Nicotine or placebo sessions occurred at least 24 hours apart.

PRT Data Reduction

Trials were excluded if response times were < 150 or > 2500 ms, or if the reaction time was ± 3SD from the mean for a given subject. A subject's data were entirely excluded if >10% of responses were outliers or if accuracy was below chance (<55%). Signal detection analysis used the following equations to calculate the discriminability and response bias, see Figure 2.

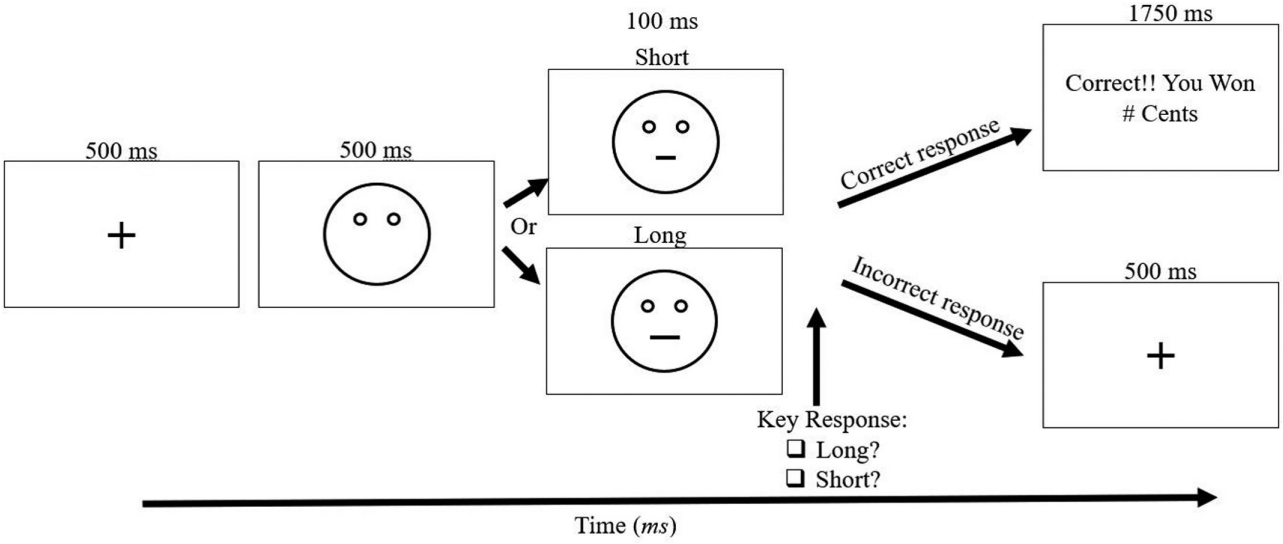

Figure 1. Depicts the probabilistic-reward task, from left to right: (1) a fixation cross is presented for 500 ms, (2) a mouth cartoon face is shown for 500 ms, (3) a long or short mouth is added to the mouthless face and shown for 100 ms, (4) participants press a key if the mouth was long (11 mm) or short (10 mm), (5) feedback is given if response was correct. Unbeknownst to the participant, one of the two mouths is reinforced three times more frequently, producing a response bias over time. [Adapted from[36].]

Table 1. Sample Characteristics

Age: M (SD), range	**20.33 (1.9), 18–24 years**
Male, *N* (%)	40 (64.7)
Race (C/AA/A/NA/MR)	44/7/6/1/6
Hispanic, *N* (%)	7 (10.2)
Age 1st Smoked, M (SD)	16.4 (2.09)
Years smoked, M (SD)	3.03 (1.88)
Cigarettes per day, M (SD)	1.76 (1.17)

M = Mean; SD = Standard deviation; C = Caucasian; AA = African American; A = Asian; NA = Native American; MR = More than one race.

$$\text{Discriminability}: \log d = \frac{1}{2} \log\left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}}\right)$$

$$\text{Response bias}: \log b = \frac{1}{2} \log\left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}}\right)$$

Figure 2. Reward sensitivity calculations. Response bias was the main variable of interest as it captures the degree to which participants implicitly learned to alter their behavior as a function of the asymmetrical reinforcement schedule.

To allow calculation in cases of a zero in the formula, 0.5 was added to every cell in the matrix. Response bias was the main variable of interest as it captures the degree to which participants implicitly learned to alter their behavior as a function of the asymmetrical reinforcement schedule. NERS was defined in terms of response bias as assessed by the PRT during NIC administration minus response bias during placebo administration.

Image Acquisition

fMRI data were collected using a Siemens Skyra 3.0 T scanner with a 20-channel head coil at Memorial Hospital in Carbondale, IL. T1-weighted structural scans in the axial plane were obtained using the Siemens default MPRAGE protocol (TR = 2200 ms, TE = 2.48 ms, flip angle 8°, 176 1.0 mm thick slices, 0.5 mm gap, FOV 230 × 230 mm). During the subsequent 8-minute resting-state functional scan (240 volumes; TR = 2000 ms, TE = 30 msec, flip angle 90°, 58 2.0 mm slices, 2.5 mm gap, FOV 220 × 220 mm), participants were instructed to keep their eyes open.

Image Processing

The FC toolbox CONN, v. 22[35] was used to process and analyze rsFC. The CONN toolbox uses the CompCor anatomical method to separate physiological noise from white matter and cerebral spinal fluid voxels, and CONN accounts for temporal lag. The default preprocessing pipeline was used and included functional realignment and unwarping, slice-timing correction, outlier identification, structural and functional segmentation and normalization, and functional smoothing. Noise components calculated from white matter and ventricles (containing cerebrospinal fluid) were removed. Motion-related data cleaning included scrubbing volumes with displacement greater than 0.5 mm. The resting-state signal was band-pass filtered from 0.008 to 0.09 Hz. The analysis used the FSL Harvard-Oxford atlas supplied with the CONN toolbox to identify regions of interest.

Statistical Analyses

The impact of NIC on discriminability and response bias was assessed using a 2 (*Drug*: placebo, NIC) × 3 (*Block*: 1, 2, 3) × 2 (*Order*: placebo first, NIC first) analysis of variance (ANOVA) and is reported in Whitton (2021).[27] Whitton (2021)[27] found NIC relative to placebo-enhanced response bias to the more frequently rewarded stimulus across all three blocks $F(1,104) = 4.11$, $p = .045$, $\eta p^2 = 0.04$.

Smoking progression was assessed using change scores from baseline to 18-month follow-up of the number of cigarettes smoked. This difference score was then $\log_{10}$ transformed to normalize the data.

For the *ROI-to-ROI* connectivity analysis of rsFC, regions of interest included the ACC, PCC, insular cortex, amygdala, PFC, hippocampus, NAcc, ventral tegmental area, and thalamus. regions of interest were examined individually and bilaterally for the ROI-to-ROI connectivity analysis, and a regression analysis was performed using the variable NERS. To control for the overall false discovery rate, all rsFC analyses were constrained to a significance level of *p*-false discovery rate < .05. Statistical regression was performed using functions native to the CONN FC toolbox.[35]

Results

Participant Characteristics

Sixty-eight young light smokers completed the PRT and had valid data for both the placebo and nicotine conditions (see Table 1). Due to no response on the 18-month smoking progression follow-up, four subjects were dropped. Participants included in the analysis had a minimum of 80% valid trials (Mean = 290; SD = 10). The smoking rates of four participants did not change from baseline, 46 decreased, and 14 increased.

FC Predictors of NERS

As displayed in Figure 3, rsFCs involving the ACC were the most frequent predictor of mean NERS. NERS was predicted by increased rsFC between the ACC and the PCC ($F(1,62) = 3.36$, p-FDR = .002, $\beta = 0.27$), In contrast, decreased rsFC between the ACC and the left inferior prefrontal gyrus (iPFG; $T(1,62) = -3.13$, p-FDR = .002, $\beta = -0.29$) and the bilateral insula ($F(2,62) = 2.02$, p-FDR = .043, $\beta = -0.17$) was associated with greater NERS. Exploratory analyses also revealed that greater rsFC between the right anterior prefrontal cortex (PFC) and the right nucleus accumbens (NAcc) predicted greater NERS in the third Block of the PRT ($T(1,62) = 3.50$, p-FDR = .001, $\beta = 0.24$). Using a Bonferroni correction for multiple comparisons, all these associations are significant at the $p < .01$ level.

FC Predictors of Smoking Progression at 18 Months

Increased smoking progression was predicted by weaker rsFC between the ACC and the combined left and right insula ($T(1,62) = -3.38$, p-FDR = .001, $\beta = -0.51$). Using a Bonferroni correction for multiple comparisons, these associations are significant at the $p < .05$ level. Figure 4 displays the relationship between smoking progression and the strength of the connectivity between the ACC and the bilateral insula.

Interaction of NERS and Smoker Progression at 18 Months

The salience network (ie, between the ACC and the insula) predicted an interaction such that those with both greater NERS and greater smoking progression had weaker salience network rsFC ($T(1,60) = -2.06$, p-FDR = .044, $\beta = -1.11$). Using a Bonferroni correction for multiple comparisons, these associations are significant at the $p < .05$ level.

Discussion

Weaker resting-state FC (rsFC) within the salience network was an important predictor of reward sensitivity and predicts smoking progression in those with the greatest NERS. Greater NERS was predicted by greater: (1) rsFC between the ACC and posterior cingulate, and (2) within the accumbens-frontal

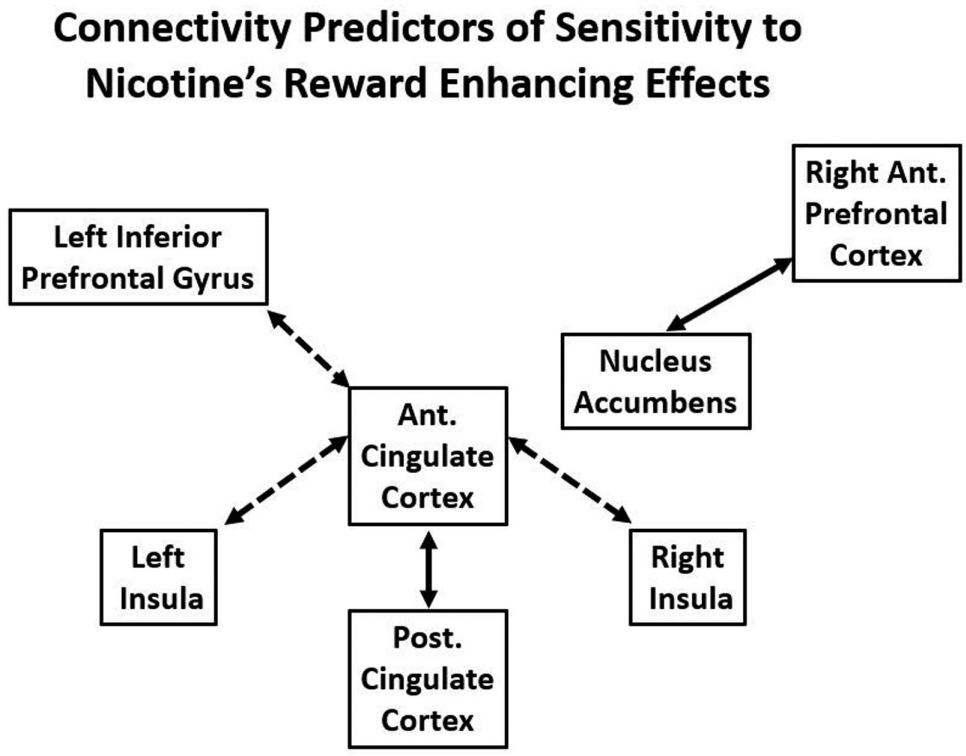

Figure 3. Greater nicotine-enhanced reward sensitivity (NERS) was predicted by greater (solid lines) functional connectivity (FC; 1) between the anterior cingulate cortex (ACC) and posterior cingulate and (2) within the accumbens-frontal reward-related regions (NAcc-right anterior PFC). Weaker (dash lines) FC between (1) the left iPFG and the ACC and (2) within the salience network (ACC and insula) also predicted greater NERS.

reward-related regions (NAcc-right anterior PFC). Weaker rsFC (1) between the left iPFG and the ACC and (2) within the salience network (ACC & insula) predicted greater nicotine-enhance reward sensitivity. The ability of rsFC between the PFC and NAcc to predict NERS but not smoking progression may reflect that the PFC and NAcc rsFC is more related to the acquisition and maintenance of optimal reinforcing learning, possibly mediated through noradrenergic and dopaminergic activity induced by the PRT.

FC Predictors of NERS

Individuals who experienced greater NERS when abstinent had a weaker degree of rsFC in areas known to be sensitive to nicotine and smoking, especially the ACC, which was the hub for one positive connection and three inverse relationships. The areas with significantly strengthened rsFC included the ACC and posterior cingulate, and within the accumbens-frontal reward-related regions (NAcc-right anterior PFC), but weaker connectivity of the left iPFG with the ACC and hubs of the salience network (ACC and insula). Importantly, these ACC connectivities align with findings in Stevens et al.'s (2020)[36] review on ACC structural connectivity involvement in reward processing, further strengthening the credibility of our observed associations.

Weaker connectivity between the left iPFG and the ACC suggests a moderating role of verbal and analytic processes of the ACC, something noted by Simmons et al., 2005.[37] Consistent with this moderating role of the left iPFG with ACC connectivity, Lerman (2014)[6] found that smoking abstinence decreased rsFC between the executive control network and the SN. Finally, our frontostriatal activation aligns with previous findings showing weaker activation in the PFC and the ACC in those with greater anhedonia symptoms.[38,39] Taken together, our weaker connectivity between the iPFG and the ACC could be a biomarker for how NIC effectively regulates attention, experience of reward, and cognitive processes.

Our finding that weaker rsFC between the bilateral insula and the ACC predicted greater NERS is consistent with the literature showing that this connection (within the salience network) is heavily involved in processing emotion and emotional salience detection.[40] The finding that greater NERS is predicted by weaker rsFC in the SN suggests nicotine's cognitive enhancing effects may be in part due to rsFC enhancement of the SN or its hubs either by enhancing risk aversion (SN[41]; insula[42,43]) and/or improving the detection and filtering of rewarding cues.[44,45] NERS was also predicted by greater rsFC between the ACC and PCC, regions that, in combination with the precuneus, constitute hubs of the default mode network,[46] and may be involved with ACC-based switching from internal DMN attentional focus to external salient (reward-related) stimuli. The high-density nicotinic cholinergic receptors in the PCC, ACC, and insula[11] could directly explain why individuals with high abstinence-state rsFC among these regions benefited more from acute nicotine administration than those with low rsFC.

Unexpectedly, only one NAcc connection was found to predict NERS, specifically a stronger rsFC between the right NAcc and the right aPFC. Individuals with high abstinence-state rsFC between the NAcc and aPFC may experience greater NERS because they have a higher density of nicotinic, glutaminergic, and/or dopaminergic receptors in the ventral tegmental area that project to the NAcc, where they promote greater dopamine release. This hypothesis is based on strong evidence indicating that nicotine-promoted dopamine release in the NAcc is caused by the stimulatory effect of nicotine on nicotinic receptors localized on afferents from the ventral tegmental area.[47] Thus, enhanced dopamine release in the aPFC may promote NERS, given that this area maintains task and context information[48] which is critical for good PRT performance. Another potential mechanism underlying the NAcc-aPFC rsFC association with NERS comes from findings indicating that PFC regulates DA release in the NAcc,[49] such that lower aPFC activation may promote greater tonic NAcc-aPFC connectivity that, in turn, promotes greater beneficial effects of acute nicotine on NERS.

FC Predictors of Smoking Progression and Moderation by NERS

Weak rsFC between ACC and bilateral insula predicted increased NIC use over the following 18 months. The

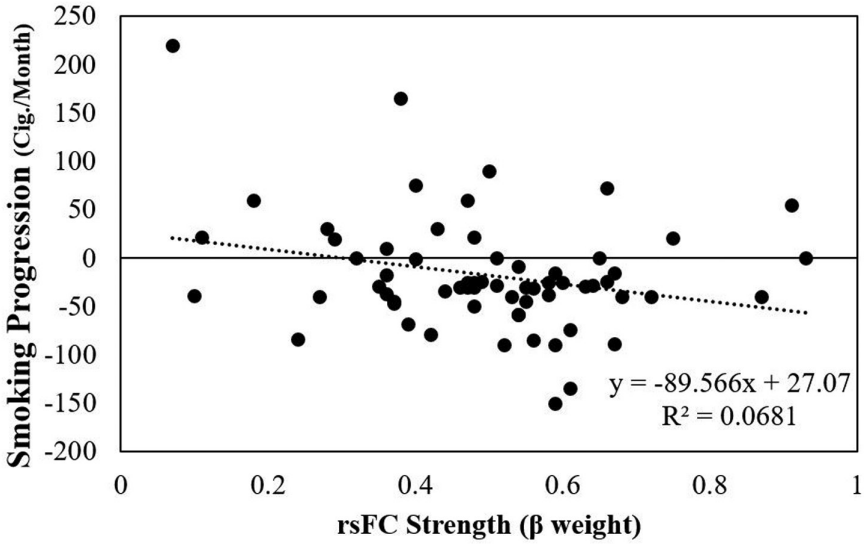

Figure 4. Weaker rsFC within the salience network (ie, between the anterior cingulate cortex and the insula) predicted greater smoking 18 months later ($T(1,62) = -3.38$, p-FDR = .001, $\beta = -0.51$).

predictive ability of weaker rsFC with hubs of the salience network aligns with previous research that identified the ACC's role in cognitive control,[50] predicting relapse in drug addiction,[51] and the insula's contribution to smoking status, withdrawal,[52] and motivation.[53] Our findings complement others showing that weak rsFC with the ACC and insula predict relapse with other drugs of abuse.[54] Moreover, our interpretations are strengthened by the discovery that weak rsFC within the SN was predicted by individuals who exhibit greater NIC-enhanced reward sensitivity and an increased frequency of NIC. This observation suggests that the weaker rsFC within the SN may contribute to both the heightened reward sensitivity and the escalation of NIC use over time. The weakened rsFC within this network may reduce the integration of cognitive control processes and the processing of salient stimuli, potentially influencing decision-making and the regulation of smoking behavior. Overall, the rsFC prediction of smoking progression suggests that weak connectivity between the bilateral insula and ACC may promote smoking progression by impacting individuals' ability to regulate their cognitive and emotional responses to smoking-related stimuli and impulses.[14] Weak rsFC between the insula and ACC may be vulnerable to smoking progression because nicotine strengthens these connections, enhancing reward and attention functions.

Conclusion

Our findings provide the first evaluation of the ability of abstinent-state rsFC to predict enhanced NERS and smoking progression in young light smokers.

Individual differences in brain regions rich with nicotinic cholinergic receptors predicted the greatest NERS and smoking progression. Our findings suggest that a weaker salience network rsFC may promote increased nicotine-induced reinforcement that leads to sustained or increased smoking. Importantly, this study adds to the literature attempting to find an intermediate phenotype of smoking relapse, a field criticized as having too few studies to perform meta-analyses.[14] Future studies might benefit by examining the predictive nature of the SN rsFC for other factors related to smoking progression, such as depressive traits and extraversion, and their interaction with NERS. Limitations of our work include the use of a limited age range of participants (18–24 years), the use of a primarily Caucasian sample, and the use of a single measure of NERS. The lack of a control group for social and racial factors related to smoking progression, for example, different risk genes vary in populations.[55–59] Most importantly, the relatively large range of cigarettes (1–5 cigarettes per day) smoked at baseline combined with the modest sample size prevented an analysis of these associations in extremely light (eg, 1 cigarette per day) versus heavier (eg, 4–5 cigarettes per day) light smokers.

Funding

Research reported in this publication was supported by R01 DA036032 from the National Institute of Drug Abuse (to DGG). DAP was partially supported by R01 MH101521 and R37 MH068376 from the National Institute of Mental Health. The content is solely the authors' responsibility and does not necessarily represent the official views of the National Institutes of Health. AEW was supported by the National Health and Medical Research Council. Investigator Grant (GNT2017521).

Declaration of Interests

For the past 30 years, Gilbert was funded by the National Institute of Drug Abuse. He has received consultation fees as an advisory board member for the Duke Center for Smoking Cessation Research and a consulting fee from Pfizer Pharmaceuticals. Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Dana Foundation, Wellcome Leap, Millennium Pharmaceuticals, and NIMH; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software; he has a financial interest in Neumora Therapeutics, which has licensed the copyright to the human version of the probabilistic-reward task through Harvard University. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors have no conflicts of interest or relevant disclosures.

Author Contributions

Matthew Gunn (Conceptualization [supporting], Formal analysis [lead], Investigation [equal], Methodology [equal], Software [equal], Writing—original draft [equal]), Gregory Rose (Conceptualization [equal], Formal analysis [supporting], Supervision [equal], Writing—review & editing [supporting]), Alexis Whitton (Conceptualization [supporting], Formal analysis [Supporting], Investigation [equal], Writing—review & editing [supporting]), Diego Pizzagalli (Conceptualization [equal], Formal analysis [supporting], Methodology [equal], Supervision [equal], Writing—review & editing [supporting]), and David Gilbert (Conceptualization [equal], Formal analysis [supporting], Funding acquisition [lead], Investigation [equal], Methodology [equal], Supervision [equal], Writing—original draft [supporting], Writing—review & editing [equal])

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Gilbert DG, Stone BM. Anhedonia in nicotine dependence. *Curr Top Behav Neurosci*. 2022;58:167–184. doi: 10.1007/7854_2022_320
2. Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: a transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. *Psychol Bull*. 2015;141(1):176–212.
3. Fedota JR, Stein EA. Resting-state functional connectivity and nicotine addiction: prospects for biomarker development. *Ann N Y Acad Sci*. 2015;1349(1):64–82.

4. Augustus Diggs H, Froeliger B, Carlson JM, Gilbert DG. Smoker-nonsmoker differences in neural response to smoking-related and affective cues: an fMRI investigation. *Psychiatry Res*. 2013;211(1):85–87.
5. McClernon FJ, Kozink RV, Lutz AM, Rose JE. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl)*. 2009;204(1):25–35.
6. Lerman C, Gu H, Loughead J, *et al*. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry*. 2014;71(5):523–530.
7. Sweitzer MM, Geier CF, Addicott MA, *et al*. Smoking abstinence-induced changes in resting state functional connectivity with ventral striatum predict lapse during a quit attempt. *Neuropsychopharmacology*. 2016;41(10):2521–2529.
8. Okuyemi KS, Harris KJ, Scheibmeir M, *et al*. Light smokers: issues and recommendations. *Nicotine Tob Res*. 2002;4(suppl 2):S103–S112.
9. Schane RE, Glantz SA, Ling PM. Nondaily and social smoking: an increasingly prevalent pattern. *Arch Intern Med*. 2009;169(19):1742–1744.
10. Levy DE, Biener L, Rigotti NA. The natural history of light smokers: a population-based cohort study. *Nicotine Tob Res*. 2009;11(2):156–163.
11. Picard F, Scavarda D, Bartolomei F. Induction of a sense of bliss by electrical stimulation of the anterior insula. *Cortex*. 2013;49(10):2935–2937.
12. Feduccia AA, Chatterjee S, Bartlett SE. Neuronal nicotinic acetylcholine receptors: neuroplastic changes underlying alcohol and nicotine addictions. *Front Mol Neurosci*. 2012;5:83. doi: 10.3389/fnmol.2012.00083
13. Garibotto V, Wissmeyer M, Giavri Z, Ratib O, Picard F. Nicotinic acetylcholine receptor density in the "higher-order" thalamus projecting to the prefrontal cortex in humans: a PET Study. *Mol Imag Biol*. 2020;22(2):417–424. doi: 10.1007/s11307-019-01377-8
14. Rabat Y, Chanraud S, Abdallah M, Sibon I, Berthoz S. Precision preventive medicine of relapse in smoking cessation: can MRI inform the search of intermediate phenotypes? *Biology*. 2021;11(1):35.
15. Janes AC, Krantz NL, Nickerson LD, Frederick BB, Lukas SE. Craving and cue reactivity in nicotine-dependent tobacco smokers is associated with different insula networks. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(1):76–83.
16. Pariyadath V, Stein EA, Ross TJ. Machine learning classification of resting state functional connectivity predicts smoking status. *Front Hum Neurosci*. 2014;8:425. doi: 10.3389/fnhum.2014.00425
17. Janes AC, Pizzagalli DA, Richardt S, *et al*. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence [published correction appears in Biol Psychiatry. 2010 May 15;67(10):1002]. *Biol Psychiatry*. 2010;67(8):722–729.
18. Hong LE, Gu H, Yang Y, *et al*. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch Gen Psychiatry*. 2009;66(4):431–441.
19. Gilbert DG, Dibb WD, Plath LC, Hiyane SG. Effects of nicotine and caffeine, separately and in combination, on EEG topography, mood, heart rate, cortisol, and vigilance. *Psychophysiology*. 2000;37(5):583–595.
20. Gilbert D, McClernon J, Rabinovich N, *et al*. Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. *Nicotine Tob Res*. 2004;6(2):249–267.
21. Gilbert DG, Izetelny A, Radtke R, *et al*. Dopamine receptor (DRD2) genotype-dependent effects of nicotine on attention and distraction during rapid visual information processing. *Nicotine Tob Res*. 2005;7(3):361–379.
22. Newhouse P, Kellar K, Aisen P, *et al*. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. *Neurology*. 2012;78(2):91–101.
23. Gilbert DG. Depression, smoking, and nicotine: toward a bioinformational situation by trait model. *Drug Dev Res*. 1996;38(3-4):267–277.
24. Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. *Biol Psychiatry*. 2008;63(11):1061–1065.
25. Pergadia ML, Der-Avakian A, D'Souza MS, *et al*. Association between nicotine withdrawal and reward responsiveness in humans and rats. *JAMA Psychiatry*. 2014;71(11):1238–1245.
26. Whitton AE, Webb CA, Dillon DG, *et al*. Pretreatment rostral anterior cingulate cortex connectivity with salience network predicts depression recovery: findings from the EMBARC randomized clinical trial. *Biol Psychiatry*. 2019;85(10):872–880.
27. Whitton AE, Rabinovich NE, Lindt JD, *et al*. Genetic and depressive traits moderate the reward-enhancing effects of acute nicotine in young light smokers. *Nicotine Tob Res*. 2021;23(10):1779–1786.
28. Pizzagalli, D. A. (2022). *Anhedonia: Preclinical, Translational, and Clinical Integration*. Switzerland: Springer International Publishing.
29. Tiwari RK, Sharma V, Pandey RK, Shukla SS. Nicotine addiction: neurobiology and mechanism. *J Pharmacopuncture*. 2020;23(1):1–7.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.
31. Gilbert DG, Jensen RA, Meliska CJ. A system for administering quantified doses of tobacco smoke to human subjects: plasma nicotine and filter pad validation. *Pharmacol Biochem Behav*. 1988;31(4):905–908.
32. Masson CL, Gilbert DG. Cardiovascular and mood responses to quantified doses of cigarette smoke in oral contraceptive users and nonusers. *J Behav Med*. 1999;22(6):589–604.
33. DiFranza JR, Savageau JA, Fletcher K, *et al*. Measuring the loss of autonomy over nicotine use in adolescents: the DANDY (Development and Assessment of Nicotine Dependence in Youths) study. *Arch Pediatr Adolesc Med*. 2002;156(4):397–403.
34. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol Psychiatry*. 2005;57(4):319–327.
35. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Con*. 2012;2(3):125–141.
36. Stevens FL, Hurley RA, Taber KH. Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci*. 2011;23(2):121–125.
37. Simmons A, Miller D, Feinstein JS, Goldberg TE, Paulus MP. Left inferior prefrontal cortex activation during a semantic decision-making task predicts the degree of semantic organization. *Neuroimage*. 2005;28(1):30–38.
38. Pizzagalli DA, Roberts AC. Prefrontal cortex and depression. *Neuropsychopharmacology*. 2022;47(1):225–246.
39. Pizzagalli D, Whitton A, Kumar P, *et al*.. *Distinct profiles of anhedonia and reward processing and their prospective associations with quality of life among individuals with mood disorders*. 2022.
40. Deen B, Pitskel NB, Pelphrey KA. Three systems of insular functional connectivity identified with cluster analysis. *Cereb Cortex*. 2011;21(7):1498–1506.
41. Markett S, Weber B, Voigt G, *et al*. Intrinsic connectivity networks and personality: the temperament dimension harm avoidance moderates functional connectivity in the resting brain. *Neuroscience*. 2013;240:98–105.
42. Feinstein JS, Stein MB, Paulus MP. Anterior insula reactivity during certain decisions is associated with neuroticism. *Soc Cogn Affect Neurosci*. 2006;1(2):136–142.
43. Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*. 2003;19(4):1439–1448.

44. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci.* 2011;15(10):483–506.
45. Seeley WW, Menon V, Schatzberg AF, *et al*. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* 2007;27(9):2349–2356.
46. Broyd SJ, Demanuele C, Debener S, *et al*. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev.* 2009;33(3):279–296.
47. Galaj E, Ranaldi R. Neurobiology of reward-related learning. *Neurosci Biobehav Rev.* 2021;124:224–234. doi: 10.1016/j.neubiorev.2021.02.007
48. Dosenbach NU, Visscher KM, Palmer ED, *et al*. A core system for the implementation of task sets. *Neuron.* 2006;50(5):799–812.
49. Del Arco A, Mora F. Prefrontal cortex-nucleus accumbens interaction: in vivo modulation by dopamine and glutamate in the prefrontal cortex. *Pharmacol Biochem Behav.* 2008;90(2):226–235.
50. Niendam TA, Laird AR, Ray KL, *et al*. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn Affect Behav Neurosci.* 2012;12(2):241–268.
51. Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH. Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. *Neuropsychopharmacology.* 2013;38(6):1085–1093.
52. Abdolahi A, Williams GC, Benesch CG, *et al*. Damage to the insula leads to decreased nicotine withdrawal during abstinence. *Addiction.* 2015;110(12):1994–2003.
53. Naqvi N.H., Bechara A. The Role of the Insula in Goal-Directed Drug Seeking and Choice in Addiction. In: Heather N., Segal G., eds. *Addiction Cho*. Oxford, UK: Oxford University Press; 2016. pp. 205–224.
54. Camchong J, Stenger A, Fein G. Resting-state synchrony during early alcohol abstinence can predict subsequent relapse. *Cereb Cortex*. 2013;23(9):2086–2099.
55. Pandey N, Pal S, Sharma LK, *et al*. SNP rs16969968 as a strong predictor of nicotine dependence and lung cancer risk in a North Indian population. *Asian Pac J Cancer Prev.* 2017;18(11):3073–3079.
56. Otto JM, Gizer IR, Bizon C, Wilhelmsen KC, Ehlers CL. Polygenic risk scores for cigarettes smoked per day do not generalize to a Native American population. *Drug Alcohol Depend*. 2016;167:95–102.
57. Bierut LJ, Stitzel JA, Wang JC, *et al*.. Variants in nicotinic receptors and risk for nicotine dependence. *Amer. J Psychiatry.* 2008;165(9):1163–1171.
58. Doyle GA, Chou AD, Saung WT, *et al*. Identification of CHRNA5 rare variants in African-American heavy smokers. *Psychiatr Genet*. 2014;24(3):102–109.
59. Sherva R, Wilhelmsen K, Pomerleau CS, *et al*.. Association of a single nucleotide polymorphism in neuronal acetylcholine receptor subunit alpha 5 (CHRNA5) with smoking status and with 'pleasurable buzz'during early experimentation with smoking. *Addiction.* 2008;103(9):1544–1552.