

Original Research

Overnight Abstinence, Ventrostriatal-Insular Connectivity, and Tridimensional Personality Traits in Cigarette Smokers

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Abstract

Background: Personality traits contribute to the risks of smoking. The striatum has been implicated in nicotine addiction and nicotine deprivation is associated with alterations in resting state functional connectivity (rsFC) of the ventral (VS) and dorsal (DS) striatum. However, it remains unclear how striatal rsFC may change following overnight abstinence or how these shorter-term changes in inter-regional connectivity relate to personality traits. **Methods:** In the current study, 28 smokers completed assessments with Fagerström Test of Nicotine Dependence, Tridimensional Personality Questionnaire (TPQ), as well as resting state functional magnetic resonance imaging (fMRI) scans during satiety and after overnight abstinence. We processed imaging data with published routines and evaluated the results with a corrected threshold. **Results:** Smokers showed increases in the VS-insula rsFC but no significant changes in the DS rsFC after overnight abstinence as compared to satiety. The difference in the VS-insula rsFC (abstinence minus satiety) was negatively correlated with harm avoidance. **Conclusions:** These findings highlighted striatal connectivity correlates of very short-term abstinence from smoking and how the VS-insula rsFC may vary with individual personality traits, interlinking neural markers and personality risk factors of cigarette smoking at the earliest stage of abstinence.

Keywords: nicotine abstinence; ventral striatum; resting state fMRI; functional connectivity; TPQ

1. Introduction

Personality traits have been identified as a risk factor of the initiation and maintenance of substance misuse, including cigarette smoking [1–3]. As assessed with the Tridimensional Personality Questionnaire (TPQ) [4,5], the traits of novelty seeking (NS), harm avoidance (HA), and reward dependence (RD) have been extensively investigated in relation to substance use. Higher NS levels have been associated with nicotine [6] and opiate and alcohol [7] use disorders. NS predicts earlier onset and severity of drinking [8,9]. Prior research has demonstrated that smokers with higher RD showed higher motivation to quit [10]. As compared to control participants, cigarette smokers [11], cocaine users [12], and people with dependent use of the internet [13] all demonstrated lower RD. In contrast, the findings on HA are less consistent. Prior research has shown higher HA in smokers than non-smokers [10,14], as well as in smokers with more severe dependence [14] and less motivation to quit [10]. However, others reported no differences [15] or lower HA in predicting earlier initiation of smoking [16], drinking [17], and other substance uses [18,19] and unsuccessful smoking cessation [20]. Thus, unlike NS and RD, each as a risk and mitigating factor, the roles of HA in substance misuse remains to be clarified [21].

Nicotine withdrawal leads to physical and mental symptoms that peak in the first 1–2 days following abstinence [22,23]. Studies have associated dimensional personality traits and withdrawal symptoms following acute nicotine abstinence. In smokers assessed each following 12-hour abstinence and ad libitum smoking, those high in NS and/or in HA reported more severe withdrawal symptoms, negative affect, and craving [24]. In smokers abstinent for 1 to 2 days, higher levels of NS and HA were correlated with lower levels of post-quit positive affect and more severe negative affect and other withdrawal symptoms, including sleep disturbance and difficulty in concentration [20]. These findings suggest that the effects of nicotine abstinence vary with individual personality traits. Understanding the neural underpinnings of the association may inform interventions to facilitate long-term abstinence.

Abundant research highlights the multiple and likely related roles of the striatum in supporting TPQ traits and pathophysiological processes of substance misuse [25]. For instance, RD was negatively correlated with gray matter volume of the caudate nucleus [26] and striatal dopamine D2 receptor specific binding in healthy adults [27]. In functional imaging, NS was associated with higher bonus-related activity in the left ventral striatum (VS) in a reward task in healthy adults [28]. Social drinkers with high



vs. low alcohol use demonstrated lower activation of the left caudate during risk-taking (i.e., speeded vs. slowed) responses in a stop signal task, which may be accounted for by individual NS trait [29]. In healthy males, NS predicted alcohol- [30] and amphetamine-elicited [31] increases in extracellular dopamine levels in the VS. Moreover, in healthy males, levels of ventral, but not dorsal, striatal dopamine synthesis capacity were significantly correlated with individual trait of NS [32]. HA was associated with dopamine transporter availability in the striatum in alcohol dependent but not control individuals [33].

The striatum has also been specifically implicated in abstinence-induced behavioral and neural reactivity in smokers. For example, bilateral caudate and medial prefrontal cortex showed higher responses to anticipation of smoking vs. monetary rewards after 24 hours of abstinence in comparison with satiety in smokers [34]. Another study found greater activation in a wide swath of cortical regions as well as the putamen and thalamus in response to smoking vs. control cues following 24 h abstinence [35]. An earlier study of female smokers reported stronger VS activity in response to smoking vs. non-smoking cues in satiety vs. overnight abstinence [36]. Studies have characterized changes in resting state functional connectivity (rsFC) of the dorsal anterior cingulate cortex during abstinence as compared to satiety in smokers [37,38]. Relative to satiety, abstinence for 24 hours elicited higher connectivity between bilateral VS and insula, superior temporal gyrus, and anterior/mid-cingulate cortex among non-relapsers, whereas the opposite was observed for relapsers during a 3-week follow-up [39].

In the current study, we examined whether seed-based rsFCs of bilateral VS and subregions of dorsal striatum (DS) (i.e., caudate, putamen, and globus pallidum) would differ between overnight abstinence and satiety in cigarette smokers and how the differences in rsFC may relate to clinical characteristics. In light of extant research, we speculated that changes in the striatal rsFC due to overnight abstinence may be correlated with individuals' TPQ traits.

2. Methods

2.1 Subjects, Informed Consent, and Assessment

Thirty-nine regular smokers (age 24–55 years) participated in the current study. The details of subject recruitment have been described in our prior work [40] and are provided in the **Supplementary material**. The study was conducted according to a protocol approved by the Institutional Review Board of Yale University (approval number: 2000022986). Written informed consent was obtained from each individual prior to the study. A final sample size of 28 (13 women) was included in the data analyses, after excluding participants who did not complete scanning ($n = 7$), smoked during the required abstinence ($n = 2$), or had excessive head motion ($n = 2$).

Participants completed one fMRI session with overnight abstinence from smoking and the other session with ad libitum smoking. The two sessions for each participant were 1–2 weeks apart and counter-balanced across subjects. Exhaled breath carbon monoxide (CO) level was tested for verification of overnight abstinence. Urine toxicology tests were performed prior to each scan for illicit substances and quantifying the cotinine levels. Before the first magnetic resonance (MR) scan, participants reported daily consumption of cigarettes, years of smoking, and nicotine addiction severity using the Fagerström Test for Nicotine Dependence (FTND; range 0–10). We computed pack years for each participant by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking to reflect lifetime exposure to tobacco. We also assessed novelty seeking, harm avoidance, and reward dependence with the TPQ [5].

Prior to each scan, we recorded the time since last cigarette in hours for each participant (i.e., abstinence duration). Twenty-one participants (13 women) were assessed for withdrawal symptoms with reference to the past 24 hours using Hughes-Hatsukami Withdrawal Questionnaire [41], craving to smoke with a brief, 10-item version of the Questionnaire of Smoking Urges [42], and state anxiety with State-Trait Anxiety Inventory [43].

2.2 Analyses of Demographic and Clinical Measures

We examined sex differences in the demographic and clinical measures with two-sample t tests. The 2 (abstinence vs. satiety) by 2 (men vs. women) mixed-model analyses of variance (ANOVAs) were performed on the CO level, withdrawal duration, withdrawal symptom severity, craving to smoke, and state anxiety. Given that the urine cotinine level was an ordinal variable, we used a nonparametric test of mixed-model ANOVA instead. We computed partial correlation coefficients between TPQ trait scores and FTND score and clinical characteristics that showed significant state differences with age as a covariate in men and women combined and separately. We used slope tests to examine the sex differences in the correlations [44–46].

2.3 MRI Data Acquisition, Preprocessing, and Group-Level Analyses

Imaging was conducted with 3.0 Tesla Prisma whole-body magnetic resonance imaging (MRI) system and 64-channel head coil (Siemens Medical Solutions, Inc., Erlangen, Germany), with scout scans, high-resolution MPAGE, and BOLD scans, as in our published work [47]. The details of MRI data acquisition are provided in the Supplement. We preprocessed the resting state fMRI data as described earlier [40,48], including realignment, co-registration, normalization, smoothing, regression of confounding signals (i.e., white matter, cerebrospinal fluid, whole-brain mean, and physiological signals), temporal band-pass filtering, and scrubbing. On average, 18.11%

and 18.79% of the time points were removed across subjects for abstinence and satiety scan, respectively. There was no significant difference in the numbers of scrubbed time points between abstinence and satiety scans ($t = 0.19$, $p = 0.848$).

As with our previous studies [45,48], the bilateral VS mask was generated by cytoarchitectonic and topographical criteria [49], and the masks of bilateral DS as well as subregions of the DS, including bilateral caudate, putamen, and pallidum were obtained from the Automated Anatomic Labeling atlas [50]. We used these masks as seed regions (Fig. 1A) to compute whole-brain rsFC. We extracted the β estimates of the regions of interest (ROIs) revealed in whole-brain rsFC analyses for each state and computed the β differences between states for linear correlations with FTND score, TPQ traits, and clinical measures that showed significant differences between states. We performed the analyses in men and women combined and separately.

3. Results

3.1 Demographics and Clinical Measures

The mean and standard deviation (SD) values of demographic and clinical measures are presented in Table 1. Two-sample t tests showed no significant sex differences in any of the demographic or clinical metrics (p 's ≥ 0.124). The 2 (state: abstinence and satiety) by 2 (sex: men and women) mixed-model ANOVAs showed a significant interaction effect on the CO level ($F = 9.91$, $p = 0.005$) but not on any other clinical measures (p 's ≥ 0.753). Simple-effect tests showed that the CO level was significantly lower in abstinence vs. satiety in women ($p < 0.001$) but not in men ($p = 0.060$) and there were no sex differences in the CO level in either abstinence ($p = 0.371$) or satiety ($p = 0.296$). The nonparametric interaction test for mixed-model ANOVA showed no state-by-sex interaction effect on urine cotinine level ($F = 0.10$, $p = 0.753$). The main effects of state were significant on the CO level, withdrawal interval, withdrawal symptom severity, and craving to smoking (p 's ≤ 0.002), but not on the cotinine level ($p = 0.753$) or state anxiety ($p = 0.060$). None of these clinical measures showed significant main effects of sex (p 's ≥ 0.148).

Across all participants, the TPQ NS, HA, or RD scores were not significantly correlated with FTND score (p 's ≥ 0.498), or any clinical measures in abstinence (p 's ≥ 0.113) or satiety (p 's ≥ 0.078). In men alone, HA score was positively correlated with withdrawal symptom severity in abstinence ($r = 0.82$, $p = 0.025$) but not in satiety ($r = 0.31$, $p = 0.501$), though slope test showed no differences in the correlation ($t = 0.33$, $p = 0.746$). In contrast, women did not show a significant correlation between HA score and withdrawal symptom severity in abstinence ($r = 0.27$, $p = 0.453$) or in satiety ($r = 0.42$, $p = 0.223$). The correlation of HA score and withdrawal symptom severity during abstinence was significantly stronger in men than in women (slope test, $t = 2.31$, $p = 0.036$). RD and FTND scores were negatively

correlated in women ($r = -0.65$, $p = 0.040$) but positively correlated in men ($r = 0.45$, $p = 0.312$) and the slope test showed significant differences in the correlation ($t = 2.16$, $p = 0.042$). None of the other correlations were significant in men and women examined together or separately.

3.2 Seed-Based Whole-Brain rsFC and Clinical Correlations

In whole-brain analyses of the full sample, paired-sample t test of state did not show any clusters with significant differences in rsFC with bilateral DS, caudate, putamen, or pallidum. With bilateral VS as a seed, the rsFC with a cluster in the left anterior insula (AI) extending to posterior orbitofrontal cortex (pOFC) and inferior frontal gyrus, pars orbitalis (IFGpo) (cluster size $k = 74$, MNI coordinates $x = -34$, $y = 22$, $z = -12$, peak $Z = 4.38$) was stronger in abstinence vs. satiety (Fig. 1B). A mixed-model sex $\times$ state ANOVA of the β showed a stronger VS-insula rsFC in abstinence vs. satiety [$F(1, 26) = 36.12$, $p < 0.001$], as expected, but no significant sex main [$F(1, 26) = 3.54$, $p = 0.071$] or interaction [$F(1, 26) = 0.87$, $p = 0.359$] effect.

Whole-brain paired-sample t tests were also performed for men and women separately. However, no clusters showed significant rsFC with bilateral VS, DS, caudate, putamen or pallidum in either men or women at the same threshold.

With age as a covariate, the difference of VS-insula rsFC between abstinence and satiety was negatively correlated with HA score in men and women combined ($r = -0.54$, $p = 0.021$). This correlation was marginally significant ($r = -0.74$, $p = 0.055$) in men alone but not significant in women alone ($r = -0.43$, $p = 0.218$), and the slope test showed no significant sex difference in the correlations ($t = 0.10$, $p = 0.918$). The difference of VS-insula rsFC between states was not significantly correlated with NS, RD, or FTND score or with the differences of withdrawal symptom severity or craving to smoke between states in all (p 's ≥ 0.190), men (p 's ≥ 0.138), and women (p 's ≥ 0.232) alone, with age as a covariate.

We also performed regressions between VS-insula rsFC and TPQ subscores and clinical measures separately for satiety and abstinence, and the results are shown in **Supplementary Table 1**. Notable were positive correlations of VS-insula rsFC with FTND scores though the correlation was significant during satiety ($r = 0.570$, $p = 0.014$) but not abstinence ($r = 0.346$, $p = 0.160$).

4. Discussion

We demonstrated altered ventrostriatal rsFC after overnight abstinence in link with personality traits in cigarette smokers. In abstinence vs. satiety, smokers showed stronger VS rsFC with left insula extending to OFC and IFGpo. Abstinence-elicited changes in VS-insula rsFC was negatively correlated with HA trait, a relationship that appeared to be driven by males. We also found higher levels

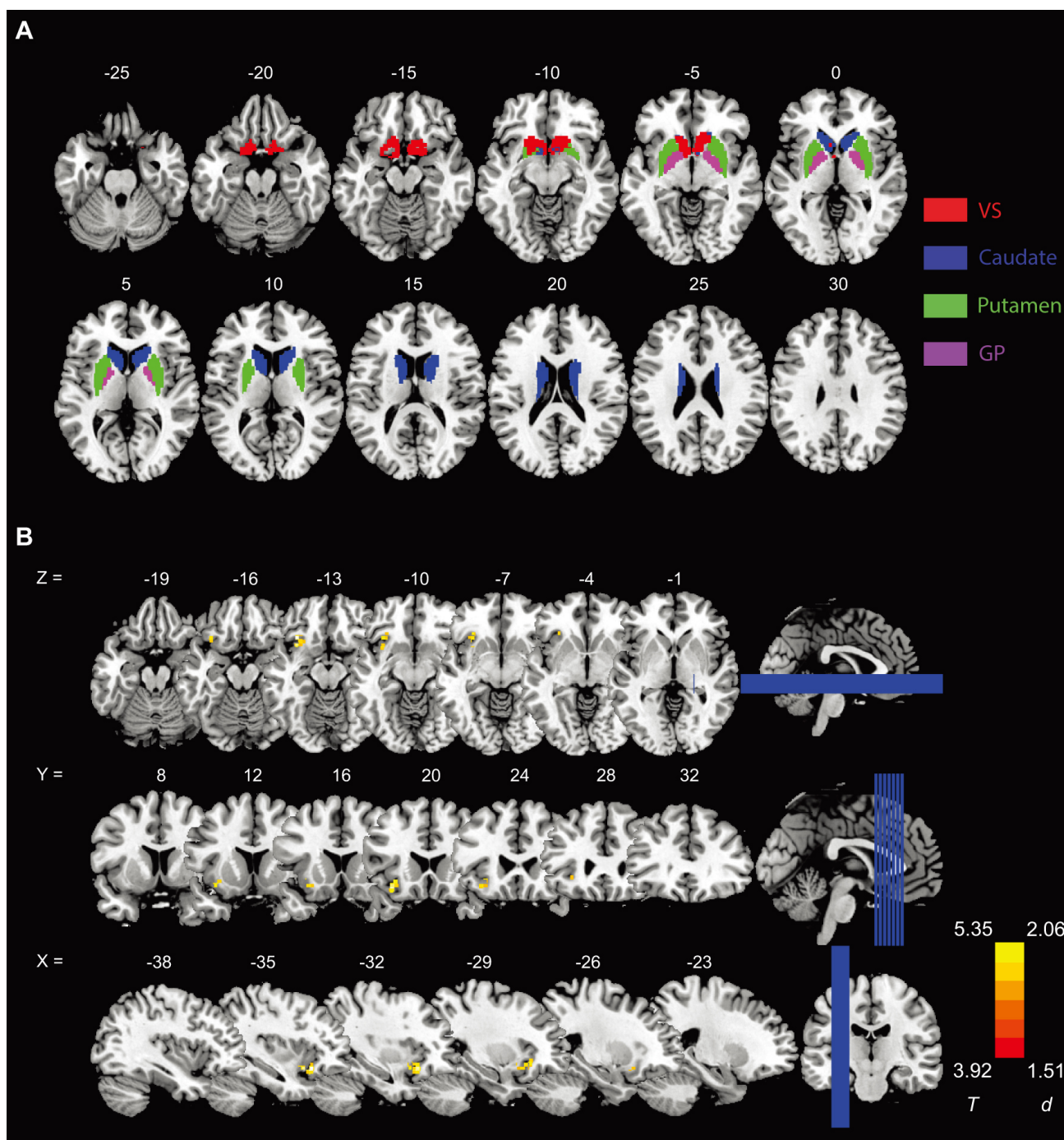


Fig. 1. Striatal masks and a cluster identified in whole-brain analysis. (A) Masks of ventral striatum (VS), caudate, putamen, and globus pallidus (GP). (B) A cluster of left insula extending to posterior OFC and IFGpo showed stronger rsFC with VS in abstinence vs. satiety. Color bar shows T value and Cohen's d for the significant cluster. OFC, orbitofrontal cortex; IFGpo, inferior frontal gyrus pars orbitalis.

of HA were associated with greater withdrawal symptom severity in abstinence for men but not women and higher levels of RD were associated with lesser nicotine dependence in women and potentially more severe nicotine dependence in men. We discussed the main findings below.

4.1 Functional Connectivity Changes in Abstinence vs. Satiety

We observed stronger VS rsFC with AI extending to pOFC and IFGpo in overnight abstinence vs. satiety, in line with an earlier study associating 24-h nicotine abstinence with higher VS rsFC with the insula, superior temporal gyrus and anterior/mid-cingulate cortex [39]. The lat-

Table 1. Demographic and clinical measures in men and women.

	Mean $\pm$ SD				Two-sample t and ANOVA	
	Men (n = 15)		Women (n = 13)		T	p
Age (years)	41.5 $\pm$ 10.5		36.5 $\pm$ 8.0		1.38	0.18
Scan interv. (d)	9.6 $\pm$ 4.9		9.5 $\pm$ 3.8		0.04	0.97
Pack year	17.9 $\pm$ 21.7		7.9 $\pm$ 6.9		1.59	0.12
FTND	4.7 $\pm$ 2.8		4.6 $\pm$ 2.4		0.05	0.96
TPQ NS	5.6 $\pm$ 2.7		4.0 $\pm$ 3.3		1.38	0.18
TPQ HA	7.9 $\pm$ 6.7		9.1 $\pm$ 5.5		−0.47	0.64
TPQ RD	4.3 $\pm$ 2.3		5.6 $\pm$ 2.5		−1.45	0.16
	Abs	Sat	Abs	Sat	F^*	p^*
CO (ppm)	10.1 $\pm$ 10.1	14.2 $\pm$ 11.7	7.0 $\pm$ 6.7	19.9 $\pm$ 13.8	36.78	<0.001
Cotinine level	5.4 $\pm$ 0.8	5.5 $\pm$ 0.8	5.4 $\pm$ 0.7	5.4 $\pm$ 1.0	0.10	0.75
Withdr. dur. (h)	10.8 $\pm$ 2.1	1.6 $\pm$ 1.7	12.2 $\pm$ 4.4	1.8 $\pm$ 3.5	391.33	<0.001
Withdr. sym.	14.3 $\pm$ 7.7	8.6 $\pm$ 5.7	11.9 $\pm$ 6.6	8.0 $\pm$ 4.9	15.19	0.001
Craving	45.5 $\pm$ 16.6	32.9 $\pm$ 13.4	49.4 $\pm$ 16.0	32.8 $\pm$ 17.5	12.57	0.002
State anxiety	40.4 $\pm$ 16.6	35.1 $\pm$ 10.8	31.7 $\pm$ 10.8	29.4 $\pm$ 8.3	4.01	0.06

Note: interv., interval; d, day; FTND, Fagerström Test for Nicotine Dependence; TPQ, Tridimensional Personality Questionnaire; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; CO, carbon monoxide; Withdr., Withdrawal; dur. (h), duration (hours); sym., symptom severity; **F* and *p* values reflect the main effects of state in the mixed-model ANOVAs.

ter study also reported decreased DS rsFC with medial prefrontal cortex, posterior cingulate cortex, hippocampus, and supplementary motor area over 24-h abstinence vs. satiety; in contrast, we did not find any significant differences in the DS connectivity in overnight abstinence vs. satiety. These findings collectively suggest altered VS-insula rsFC at the very early stage of abstinence, which may be followed by changes in DS rsFC. Of note, Sweitzer, Geier [39] demonstrated elevated VS rsFC in non-relapsers but the opposite in relapsers at 3 weeks of follow-up and the same patterns of changes in DS rsFC across both groups, associating altered VS but not DS connectivity during early abstinence with smoking cessation outcomes.

Neurobiological models of addiction implicated both striatum and insula in the addictive processes of bingeing/intoxication, withdrawal/negative affect, and craving [51,52]. Previous research demonstrated lower VS-insula connectivity in non-treatment-seeking cocaine users as compared with healthy controls [53]. Here, we observed that overnight abstinence induced higher VS connectivity with the insula extending to pOFC and IFGpo, implicating the striato-insula and corticostriatal circuits during acute withdrawal. The striato-insula circuit underlies motivation and reward processing, integration of affective and cognitive function, as well as action selection and planning [54,55]. The striato-insula circuit may support the motivation to use drugs as a result of aversive bodily states in abstinence [56]. Unexpectedly, we did not find any significant correlations between changes in VS-insula rsFC and withdrawal symptom severity or craving to smoke, likely because of the small sample size and/or relatively low levels of nicotine dependence of the participants. Note

that the VS-insula rsFCs were positively correlated with FTND scores (**Supplementary Table 1**), suggesting VS-insula rsFC as a feature of smoking problem. Thus, if verified, those with more severe smoking problem would show higher VS-insula rsFC and VS-insula rsFC would become even stronger during withdrawal.

4.2 Relationships of TPQ Traits with Clinical Measures and VS-Insula rsFC

We found higher levels of HA trait in association with more severe withdrawal symptoms during overnight abstinence in men but not in women, with sex differences confirmed by the slope test. An animal study found that nicotine withdrawal was accompanied by a significant and persistent loss of striatal serotonergic activity, starting from initial abstinence [57]. The HA trait, as characterized by excessive worrying, pessimism, shyness, fearfulness, doubtfulness, and easy fatigability is related to low serotonergic activity [58,59]. We speculate that striatal serotonergic activity may play a role in supporting sex differences in the relationships between HA trait and withdrawal symptom severity, an issue that can be investigated with molecular imaging in humans as well as imaging and electrophysiology in rodent models. Our findings are also largely in line with prior evidence demonstrating that HA predicted 12-h nicotine abstinence-induced increases in negative affect and urges to smoke [24]. We also observed that RD was negatively correlated with FTND scores in women, in accord with social detachment and insensitivity to social approval as a risk factor of substance misuse [7,60]. In contrast, men showed positive though non-significant correlation between RD and FTND score, consistent with a study

associating RD with craving in response to both smoking and stress vs. neutral cues [61]. Our findings suggest sex as a critical factor to consider in studies of the influences of RD traits on substance use and misuse.

Prior research has demonstrated sex differences in resting state network connectivities in smokers. For instance, women vs. men showed stronger functional coupling of the hippocampus/amygdala with bilateral AI, rostral anterior cingulate cortex, and inferior parietal lobule [62] and greater connectivity within the default mode network but no significant differences in the connectivity within the reward (i.e., striatum and orbitofrontal cortex) network [63]. Although we did not observe that men and women differed in VS whole-brain connectivity, we showed that higher HA was associated with less abstinence-induced changes in VS-insula rsFC, a relationship that appeared driven by males, consistent with earlier findings that people with higher HA showed lower regional rsFCs and insular-opercular network efficiency during resting [64]. Both the VS [65] and insula [66] showed higher activity during risk-taking decisions in positive correlation with HA. Moreover, the potential sex difference indicates that sex may modulate the relationship between HA trait and abstinence-related changes in VS-insula rsFC. In our sample, men smoked more heavily and had greater pack years as compared to women. A larger sample with men and women well-matched in nicotine use metrics may help in investigating this issue further. On the other hand, male smokers higher in HA experienced more severe withdrawal symptoms and across subjects VS-insula rsFC was positively correlated with FTND score at baseline. Thus, the findings suggest that VS-insula rsFC may reflect a relatively stable marker of individuals high in HA—likely in relation to the psychological processes of risk taking—that is not impacted by acute withdrawal from smoking.

We also observed higher levels of RD trait in association with less severe nicotine dependence in women and potentially the opposite in men. A meta-analysis on sex differences in TPQ traits in healthy individuals found that women scored higher in RD than men, reflecting stronger female endorsement of social desirability [67]. Furthermore, women with lower RD scores may show difficulties in social attachment and greater susceptibility to depression or adjustment problems [68–70], which in turn is associated with nicotine misuse. Together with our finding that speaks to the potentially contrasting, sex-specific roles of RD in substance misuse, men may engage in drinking and smoking to seek social approval and interaction whereas women do so because of social distancing and isolation. More research is needed to explore this hypothesis.

4.3 Limitations of the Study

The current study has several limitations. First, our findings are of a small sample size and preliminary. In particular, the smokers showed low-to-moderate levels of

dependence, and it remains unclear whether the findings would replicate in heavier smokers. Secondly, male vs. female smokers showed higher pack years and more (though not significantly different) severe withdrawal symptoms in our study. A better-matched cohort of men and women may help in confirming the findings. Finally, changes in striatal connectivity may be associated with motivation to quit and other psychological processes involved in chronic smoking. Longitudinal studies and more thorough clinical and behavioral assessments are needed to expand on the findings.

5. Conclusions

In conclusion, we found elevated VS-insula connectivity during overnight abstinence, with the changes in negative correlation with the individual trait of harm avoidance. These findings provide evidence to show associations between nicotine dependence, neuroadaptations in the striatal-insula network, and personality traits, which have important implications for understanding mechanisms contributing to vulnerability of drug relapse. Our findings are relevant not only to nicotine addiction but also to substance misuse as a whole and may inform neuroscience-based treatment options.

Availability of Data and Materials

The data and codes will be shared on request to the corresponding author.

Author Contributions

YC and CL designed the research study. YC performed the research and analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted according to a protocol approved by the Institutional Review Board of Yale University (approval number: 2000022986). Written informed consent was obtained from each individual prior to the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2203066>.

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