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Relating individual differences in nicotine dependence severity to underpinning motivational and pharmacological processes among smokers from vulnerable populations

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A R T I C L E I N F O

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Relative reinforcing value
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Fagerström test for nicotine dependence
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A B S T R A C T

We examined whether elucidating underpinning smoking motivation and related pharmacological processes enhances understanding of nicotine dependence among smokers from vulnerable populations. Data were obtained between Oct, 2016 and Sept, 2019 from 745 adult smokers with co-morbid psychiatric conditions or socioeconomic disadvantage at University of Vermont, Brown University, Johns Hopkins University. Smoking motivation was assessed using the Cigarette Purchase Task (CPT), a behavioral-economic task that models the relative reinforcing value of smoking under varying monetary constraint. Dependence severity was measured using the Heaviness of Smoking Index (HSI), Fagerström Test for Nicotine Dependence total scores (FTND), and FTND total scores minus items 1 and 4 ($FTND_{2,3,5,6}$). We also assessed associations between dependence severity and smoking motivation with nicotine levels and metabolism rate. Principal Component Analysis was used to examine the latent structure of the conventional five CPT indices; bivariate and multivariable modeling was used to test associations. Factor analysis resulted in a two-factor solution, Amplitude (demand unconstrained by price) and Persistence (price sensitivity). CPT latent factors were associated with each dependence-severity measure ($ps \leq 0.0001$), with associations stronger for Amplitude than Persistence across each, especially HSI which was exclusively associated with Amplitude. Amplitude and each dependence measure were associated with nicotine intake ($ps \leq 0.0002$); Persistence was not ($p = .19$). Demand Amplitude more than Persistence appears key to understanding individual differences in dependence severity. Regarding potential application, the results suggest a need for interventions that more effectively target demand Amplitude to make greater headway in reducing smoking in vulnerable populations.

Trial Registration: clinicaltrials.gov identifiers: NCT02232737, NCT02250664, NCT02250534.

1. Introduction

Tremendous progress has been made in reducing cigarette smoking among the more affluent and well educated, but less among those with comorbid psychiatric conditions or socioeconomic disadvantage (Higgins et al., 2019; Shroeder, 2016; US DHHS, 2014). There is considerable evidence that nicotine dependence severity is the strongest predictor of difficulties quitting smoking (Baker et al., 2007; Borland et al., 2010; Heatherton et al., 1989). More specifically, time to first cigarette upon waking and number of cigarettes per day as assessed by the Heaviness of Smoking Index (HSI) (Heatherton et al., 1989; Kozlowski et al., 1994) are the strongest predictors of smoking-cessation (Baker et al., 2007; Borland et al., 2010). Fagerström Test for Nicotine Dependence (FTND) total scores, which includes the two items comprising the HSI, and FTND total scores excluding the two HSI items (referred to below as $FTND_{2,3,5,6}$) also predict cessation, just less

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Table 1
Six items comprising the Fagerström Test for Nicotine Dependence (FTND).

1. How soon after you wake do you smoke your first cigarette?
   Within 5 min, 6 to 30 min, 31 to 60 min, after 60 min
2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., church, library, cinema)?
   No Yes
3. Which cigarette would you hate most to give up?
   The first one in the morning any other
4. How many cigarettes per day do you smoke?
   10 or less, 11–20, 21–30, 31 or more
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   No Yes
6. Do you smoke when you are so ill that you are in bed most of the day?
   No Yes

Taken from Heatherton TF, Kozlowski LT Frecker RC (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 86:1119–27.

effectively than the HSI (Baker et al., 2007; Fagerström et al., 2012).

Better understanding individual differences across the three forms in which the FTND has been used to predict smoking-cessation outcomes (HSI, FTND, $FTND_{2,3,5,6}$) has the potential to enhance understanding of nicotine dependence and perhaps facilitate development of more targeted and efficacious interventions. The FTND consists of six items (Table 1), with the three forms mentioned above placing different emphasis on the two items quantifying consumption: time to first cigarette upon waking (item 1) and number of cigarettes smoked/day (item 4). The FTND includes those items along with four others, two assessing smoking despite illness or rules prohibiting smoking (items 2 & 6) and two assessing preference for morning smoking suggestive of physical dependence/withdrawal (items 3 & 5). $FTND_{2,3,5,6}$ excludes the two consumption items while retaining the other four (items 2,3, 5, 6). Including the three forms in the present study allows parsing of how these item combinations alter associations between dependence severity and underpinning motivational and pharmacological processes.

In the spirit of the U.S. National Institute of Mental Health's Research Domain Criteria (RDoC) initiative (National Institute of Mental Health, 2019), which recommends characterizing psychiatric disorders in terms of underpinning psychological/biological processes rather than symptoms, we examined how the three forms of the FTND map onto differences in the relative reinforcing value of smoking and related pharmacological processes. We focused on the reinforcement process because of the broad scientific consensus that chronic smoking is largely attributable to the reinforcing effects of nicotine (Prochaska and Benowitz, 2019; US DHHS, 1988). We examined total nicotine exposure levels and nicotine metabolism rate because of their documented association with dependence risk (Benowitz, 2008). Lastly, we focused on smokers with co-morbid psychiatric conditions or socioeconomic disadvantage because smoking and nicotine dependence are overrepresented in these groups and they benefit less than healthier and more affluent smokers from tobacco control and regulatory efforts to reduce smoking (Higgins et al., 2019; Shroeder, 2016).

We assessed the relative reinforcing value of smoking using the Cigarette Purchase Task (CPT), a behavioral-economic task that asks smokers to estimate likely cigarette consumption rate and expenditure under escalating price constraints (Jacobs and Bickel, 1999). The CPT is highly sensitive to individual differences in the relative reinforcing value of smoking (referred to as 'demand' in behavioral-economic parlance), including differences by nicotine dependence severity (e.g., Gonzalez-Roz et al., 2019; Zvorsky et al., 2019). Relative reinforcing value of smoking is typically characterized by five CPT indices: (1) demand Intensity (consumption when cigarettes are free or unconstrained); (2) O_{max} (maximal expenditure on cigarettes); (3) P_{max} (price at which demand for cigarettes begins decreasing proportional to price increases); (4) Breakpoint (price at which one forgoes smoking rather than incur the cost); (5) Elasticity (overall price sensitivity). To reduce potential problems of collinearity when using five indices, we used factor analysis to investigate their latent-factor structure. Prior studies indicate that the CPT indices typically reduce to two factors: Amplitude and Persistence, with demand Intensity loading exclusively onto Amplitude and each of the other indices onto Persistence (Bidwell et al., 2012; Gonzalez-Roz et al., 2020; O'Connor et al., 2016). The same two-factor structure has also been reported with alcohol and marijuana purchase tasks (Aston et al., 2017; MacKillop et al., 2009). Based on results from a prior study (Higgins et al., 2018) and literature review (Zvorsky et al., 2019) from our group suggesting that demand Intensity is especially sensitive to individual differences in smoking related outcomes, we hypothesized that dependence severity would have a stronger association with CPT Amplitude than Persistence.

Regarding pharmacological processes, the genetically variable CYP2A6 enzyme metabolizes nicotine into its primary metabolite cotinine (COT), which is further metabolized exclusively by CYP2A6 into 3′-hydroxycotinine (3-HC). We used combined COT and 3-HC (COT + 3-HC) levels to represent total nicotine intake, hypothesizing that intake would be positively associated with nicotine-dependence severity and have a stronger association with CPT Amplitude than Persistence. The nicotine metabolism ratio (NMR) (3-HC/COT) is a noninvasive CYP2A6 phenotypic measure and a proxy for total nicotine clearance (Chenoweth et al., 2016; Dempsey et al., 2004; Nakajima et al., 1996; Rubinstein et al., 2013). We used NMR to investigate associations between nicotine metabolism, dependence severity, and CPT factor scores. We did not have a specific hypothesis on NMR given the considerable variability sometimes observed when relating NMR to nicotine dependence (Schnoll et al., 2014).

2. Methods and materials

2.1. Study sample

Participants in this multisite study (University of Vermont, Brown University, Johns Hopkins University) were 745 adult daily smokers who provided written informed consent to participate in one of three parallel, randomized controlled trials examining reduced nicotine content cigarettes in vulnerable populations. The present study uses data from trial baseline assessments. Assessments were conducted without restrictions on smoking.

Study inclusion-exclusion criteria were the same as those used previously in these same vulnerable populations (Higgins et al., 2017). Briefly, all participants had to report daily smoking of ≥ five cigarettes for ≥1 year with limited current use of other tobacco products (< 10 days in past month), no current illicit drug use other than marijuana, no intention to quit smoking within the next 30 days, and CO sample > 8 ppm. Inclusion criteria specific to smokers with affective disorders were males and females ages 18–70 years, who met Mini-International-Neuropsychiatric-Interview (Sheehan et al., 1998) criteria for current or past-year affective disorder; opioid-dependent smokers were males and females ages 18–70 years who were currently receiving opioid-maintenance treatment and stable on their maintenance dose; women of reproductive age were females only, ages 18–44 years, with highest degree ≤ high school.

2.2. Behavioral measures

Behavioral measures were obtained from all participants. Participants completed the FTND and a tobacco-history questionnaire at study intake. HSI scores were calculated by summing the scores from FTND items 1 and 4 (range: 0–6); FTND total scores represent the sum of items 1–6 (range: 0–10); and $FTND_{2,3,5,6}$ total scores represent the sum of items 2,3,5,6 (range: 0–4).

The CPT task has participants estimate how many cigarettes they would smoke in a 24-h period across escalating hypothetical prices

(Jacobs and Bickel, 1999). Prior studies have shown that results are functionally congruent across versions where participants consume purchased cigarettes and the hypothetical version used in the present study where participants simply estimate consumption (Nighbor et al., 2020; Wilson et al., 2016). Participants were instructed to imagine making purchases in a context where they have (a) the same income/savings as they do currently, (b) no access to cigarettes or nicotine products other than those offered at these prices, (c) that they would smoke the cigarettes purchased over the next 24 h, and (d) are unable to save or stockpile cigarettes. Twenty prices per cigarette were assessed: $0.00, $0.02, $0.05, $0.10, $0.20, $0.30, $0.40, $0.50, $0.60, $0.70, $0.80, $0.90, $1.00, $2.00, $3.00, $4.00, $5.00, $10.00, $20.00, and $40.00. At each price, participants were also informed how that price per cigarette translates to price per pack.

2.3. Nicotine exposure and metabolism

Blood samples were obtained from 519 participants across sites who agreed to have blood drawn and had an accessible vein. Samples were collected during the baseline assessment following usual ad-lib smoking and stored at −80 °C. The NMR was calculated as the ratio of COT over 3HC where COT and 3HC levels were assessed by LC-MS/MS with limits of quantification of ≤1 ng/ml (Nakajima et al., 1996; St. Helen et al., 2012; Tanner et al., 2015). Only samples with COT over 10 ng/ml were used in the NMR, and 3HC values below the limit of detection (LOD of 1 ng/ml) were replaced with LOD/√2 (Hornung and Reed, 1990; Lerman et al., 2015). Objective biomarkers of nicotine intake (COT + 3HC) were assessed. COT + 3HC is more accurate than COT alone due to COT's variable metabolism by CYP2A6, which results in disproportionately higher levels of COT per intake in those with slower CYP2A6-mediated COT metabolism (Zhu et al., 2013).

2.4. Data analysis

CPT consumption estimates were checked for non-systematic cases (Stein et al. (2015), resulting in exclusion of 11 participants. CPT indices were empirically derived as follows: To derive overall Elasticity (α), individual demand curves were fitted using an exponential demand equation (Hursh and Silberberg, 2008) and a GraphPad Prism template (GraphPad Software, www.graphpad.com):

$$\log Q = \log Q_0 + k\,(e^{-\alpha(Q_0 \cdot C)} - 1)$$

where Q is consumption at each price (i.e., C), Q_0 is consumption when cost is zero (converted to $0.01 for curve fitting in log-log space), k is the range of consumption in logarithmic units (calculated as the difference of the logarithms of the maximum and minimum consumption values plus 0.5), and α is the rate of change in elasticity across the demand curve. Four of the five CPT demand indices mentioned above (Intensity, O_{max}, P_{max}, Breakpoint) were derived empirically from consumption data. All demand indices were $\log_{10}$ transformed to meet normality assumptions. Index values greater than 3.29 standard deviations from the mean were designated as outliers and winsorized to one unit below the next lowest value or one unit above the next highest value (Mackillop et al., 2016; Tabachnick and Fidell, 2007).

Principal Component Analysis with oblique (oblimin) rotation was used to examine the latent factor structure of the CPT indices. Along with the other four CPT demand indices, 1/Elasticity was used in the analysis to facilitate a more intuitive interpretation of the factor structure. CPT demand indices that had loadings > 0.40 based on standardized regression coefficients were determined to have loaded onto a particular factor.

NMR was calculated as the ratio of COT over 3HC (Nakajima et al., 1996; St. Helen et al., 2012; Tanner et al., 2015). Briefly, COT and 3HC levels were assessed by LC-MS/MS with limits of quantification of ≤1 ng/ml; only samples with cotinine over 10 ng/ml were used in the NMR, and 3HC values below the limit of detection (LOD of 1 ng/ml) were replaced with LOD/√2 (Hornung and Reed, 1990) as before (Lerman et al., 2015). Objective biomarkers of nicotine intake, COT + 3HC and COT alone were assessed.

Linear regression was used for bivariate testing of associations between dependence-severity measures and CPT factor scores. Multivariable ANCOVA models were used for testing associations between dependence-severity measures and CPT factor scores, while controlling for potential confounders. Because of the different eligibility criteria used across the three vulnerable populations included in the study, vulnerable population was included as a covariate. To identify potential demographic covariates, we compared characteristics of the study sample when divided into low, moderate, and severe dependence severity using and HSI previously established cut-points in a U.S. nationally representative survey (Schnoll et al., 2014). Sex, age, education, and marital status differed at $p < .05$ and were included as covariates. Dependence-severity measures and CPT factor scores were treated as independent and dependent variables, respectively. Multivariable models were also used for testing associations between COT + 3HC, NMR and dependence-severity measures and between COT + 3HC, NMR and each CPT latent factor. Significant associations between an independent variable and either CPT latent factor were followed with a mediational analysis wherein the other CPT latent factor was forced into the model. Significant mediation was inferred if including the other CPT latent factor in the model rendered the original association non-significant ($p > .05$) (i.e., the original association was accounted for by the other CPT latent factor) (Kraemer et al., 2001). All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and with alpha set at $p < .05$ (SAS Institute Inc, 2017).

3. Results

3.1. Participants

Participants were on average 35.68 years of age, and majority female (70.87%) and non-Latino White race/ethnicity (81.87%), with ≤ high school education (52.35%) and most never married (59.33%) (Table 2). Regarding smoking characteristics, participants reported smoking an average of 17.78 ± 9.24 cigarettes/day, with breath CO levels of 17.90 ± 9.75 ppm, and mean HSI total score of 3.48 ± 1.55, FTND total score of 5.5 ± 2.37, and $FTND_{2,3,5,6}$ total score of 2.08 ± 1.17.

3.2. CPT demand curve, indices, and latent factors

The CPT aggregate demand function was well described by the modified exponential equation (Fig. 1). Individual demand curves were also well described by the exponential equation with a median R^2 of 0.79 (IQR = 0.64–0.93).

The CPT indices showed that on average participants estimated they would (a) smoke 21.74 cigarettes per day if they were free (Intensity), (b) spend a maximum of $12.98 on cigarettes in a 24-h period (O_{max}), (c) move from inelastic to elastic demand when price reached $1.51/cigarette or $30.15/pack ($P_{max}$), (d) forego smoking completely when price reached $2.51/cigarette or $50.20/pack (Breakpoint), with (e) an overall sensitivity to price of 0.0033 (Elasticity). The factor analysis resulted in the hypothesized two-factor solution of Amplitude and Persistence. Demand Intensity loaded exclusively onto Amplitude and each of the other indices loaded exclusively onto Persistence (Table 3). This two-factor solution accounted for 80% of the variance in the intercorrelational matrix of the five indices.

3.3. Associations between dependence severity and CPT factor scores

The three dependence-severity measures were positively associated with Amplitude and Persistence factor scores in bivariate analyses, with

Table 2
Participant characteristics.

Characteristics	All (*n* = 745)	Participant populations[a]		
		Affective disorders (*n* = 258)	Opioid dependent (*n* = 249)	Disadvantaged women (*n* = 238)
Age (M ± SD)	35.68 ± 11.18	37.30 ± 13.33	38.53 ± 10.54	30.96 ± 7.03
Gender (% female)	528 (70.87)	152 (58.91)	138 (55.42)	238 (100)
Race/ethnicity				
Non-Latino white	605 (81.87)	215 (83.66)	202 (82.45)	188 (79.32)
Non-Latino black	67 (9.07)	13 (5.06)	22 (8.98)	32 (13.50)
Latino	22 (2.98)	14 (5.45)	6 (2.45)	2 (0.84)
Non-Latino other or > 1 race	36 (4.87)	12 (4.67)	11 (4.49)	13 (5.49)
Non-Latino American Indian/Alaskan native	6 (0.81)	3 (1.17)	3 (1.22)	0 (0)
Non-Latino Asian	2 (0.27)	0 (0)	0 (0)	2 (0.84)
Non-Latino Hawaiian	1 (0.14)	0 (0)	1 (0.41)	0 (0)
Education				
8th grade or less	16 (2.15)	2 (0.78)	12 (4.82)	2 (0.84)
Some high school	82 (11.01)	15 (0.81)	35 (4.06)	32 (13.45)
High school graduate/equivalent	292 (39.19)	71 (27.52)	117 (46.99)	104 (43.70)
Some college	255 (34.23)	92 (35.66)	64 (25.70)	99 (41.60)
2-year Associate's degree	36 (4.83)	25 (9.69)	10 (4.02)	1 (0.42)
College graduate/4-year degree	48 (6.44)	38 (14.73)	10 (4.02)	0 (0)
Graduate or professional degree	16 (2.15)	15 (5.81)	1 (0.40)	0 (0)
Marital status				
Married	107 (14.36)	34 (13.18)	26 (10.44)	47 (19.75)
Never married	442 (59.33)	152 (58.91)	155 (62.25)	135 (56.72)
Divorced or separated	180 (24.16)	67 (25.97)	59 (23.69)	54 (22.69)
Widowed	16 (2.15)	5 (1.94)	9 (3.61)	2 (0.84)
Cigarettes smoked per day (M ± SD)	17.78 ± 9.24	15.73 ± 8.41	22.61 ± 9.86	14.98 ± 7.26
Primary smoker of mentholated cigarettes	322 (44.60)	105 (42.51)	111 (46.06)	106 (45.30)
Age started smoking regularly (M ± SD)	16.13 ± 4.06	16.72 ± 4.31	15.67 ± 4.66	15.97 ± 2.90
Breath CO level (M ± SD)	17.90 ± 9.75	18.17 ± 10.66	19.55 ± 9.97	15.91 ± 8.04
Nicotine metabolite ratio (M ± SD)	0.47 ± 0.24	0.48 ± 0.25	0.48 ± 0.23	0.44 ± 0.24
Heaviness of smoking index (M ± SD)	3.48 ± 1.55	3.16 ± 1.60	4.22 ± 1.33	3.04 ± 1.44
Fagerström test for cigarette dependence (M ± SD)	5.55 ± 2.37	5.22 ± 2.43	6.62 ± 2.03	4.79 ± 2.23
Fagerström test for cigarette dependence, minus items 1 & 4 (M ± SD)	2.08 ± 1.17	2.06 ± 1.14	2.41 ± 1.15	1.75 ± 1.15

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

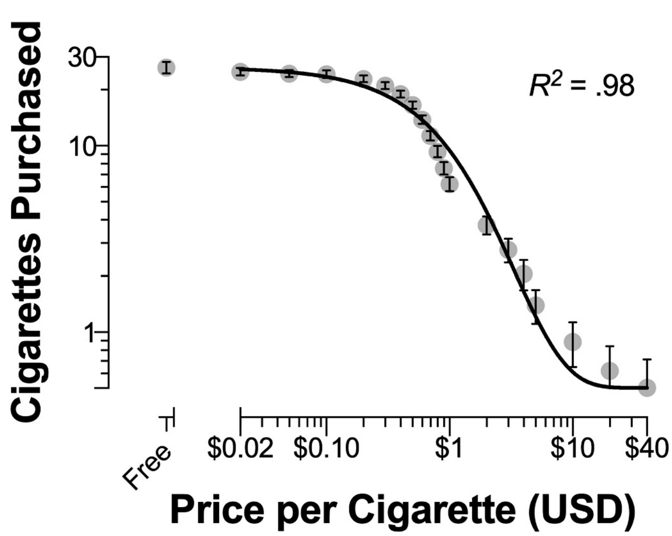

Fig. 1. Shown is an overall Cigarette Purchase Task demand curve representing the number of cigarettes purchased as a function of increasing price. R^2 represents the fit to the data of the Exponential Demand Equation (see text for details) and bars represent ± SEM.

Table 3
Cigarette purchase task mean index scores and latent factor loadings.

Index scores	Mean (95% C.I.)	Latent factor loadings	
		Amplitude EV = 0.99 Var = 20%	Persistence EV = 3.02 Var = 60%
Intensity[a]	21.74 (20.85, 22.67)	0.98	0.01
*O*max[a]	12.98 (12.03, 14.01)	0.28	0.84
Breakpoint[a]	2.51 (2.26, 2.78)	−0.11	0.95
Pmax[a]	1.51 (1.35, 1.68)	−0.17	0.98
Elasticity[a]	0.0033 (0.0030, 0.0038)	0.10	0.57

EV: eigenvalue.
[a] Back-transformed from log 10.

associations consistently stronger for Amplitude than Persistence across each measure as hypothesized, especially the HSI and FTND (Table 4, Fig. 2). Increasing HSI, FTND, and $FTND_{2,3,5,6}$ total scores accounted for 38%, 30%, and 10% of the variance in Amplitude factor scores, respectively, compared to 5%, 7%, and 6% of the variance in Persistence. Said differently, combining the two HSI items with four additional items in generating FTND total scores resulted in accounting for 8% less variance in Amplitude and only 2% more in Persistence than HSI; omitting the two consumption items and relying exclusively on the four items related to refraining from smoking and possible physical dependence/withdrawal resulted in the $FTND_{2,3,5,6}$ accounting for 28% less variance in Amplitude and only 1% more in Persistence compared to the HSI.

That pattern remained unchanged in multivariable testing. HSI total scores were significantly associated with Amplitude ($F(1,732) = 318.55, p < .0001, \eta^2 = 0.26$) and Persistence ($F(1,732) = 14.87, p = .0001, \eta^2 = 0.02$); FTND total scores were significantly associated with Amplitude ($F(1,732) = 204.50, p < .0001, \eta^2 = 0.19$) and Persistence ($F(1,732) = 25.53, p < .0001, \eta^2 = 0.03$); and $FTND_{2,3,5,6}$ total scores were significantly associated with Amplitude (F

Table 4
Correlations between CPT latent factors and indices with dependence severity measures.

	Correlation with HSI score	Correlation with FTND total score	Correlation with $FTND_{2,3,5,6}$ total score
Amplitude	0.62****	0.54****	0.28****
Persistence	0.22****	0.26****	0.23****
Intensity	0.59****	0.53****	0.28****
Omax	0.39****	0.39****	0.28****
Breakpoint	0.12***	0.18****	0.21****
Pmax	0.09*	0.15****	0.19****
Elasticity	−0.23****	−0.21****	−0.12**

**** $P < .0001$.
*** $P < .001$.
** $P < .01$.
* $P < .05$.

(1,732) = 32.14,p < .0001,η^2 = 0.04) and Persistence (F (1,732) = 22.52,p = .0001,η^2 = 0.03). The strength of these associations was consistently greater for Amplitude than Persistence across the three measures but especially the HSI and FTND total scores. η^2 values represent the proportion of variance accounted for by the predictors, meaning that increasing HSI, FTND, and $FTND_{2,3,5,6}$ total scores accounted for 26%, 19%, and 4% of the variance in Amplitude, respectively, compared to 2%, 3%, and 3% of the variance in Persistence. As noted regarding the bivariate analysis, FTND total scores accounted for 7% less variance in Amplitude and 1% more in Persistence compared to the HSI; and by omitting the two consumption items, $FTND_{2,3,5,6}$ accounted for 22% less variance in Amplitude and 1% more in Persistence compared to the HSI.

The only instance of significant mediation between the three measures of dependence severity and HSI latent factors was for the relationship between HSI total scores and Persistence. When Amplitude was included in that model, the association was no longer significant, with the *p* value increasing from the original p = .0001 to *p* = .13.

3.4. Associations between dependence severity and CPT factor scores with nicotine intake and metabolism rate

In multivariable models, each of the dependence-severity measures were significantly associated with COT + 3HC levels, with the strength of association greatest with HSI total scores (F(1, 517) = 69.83,

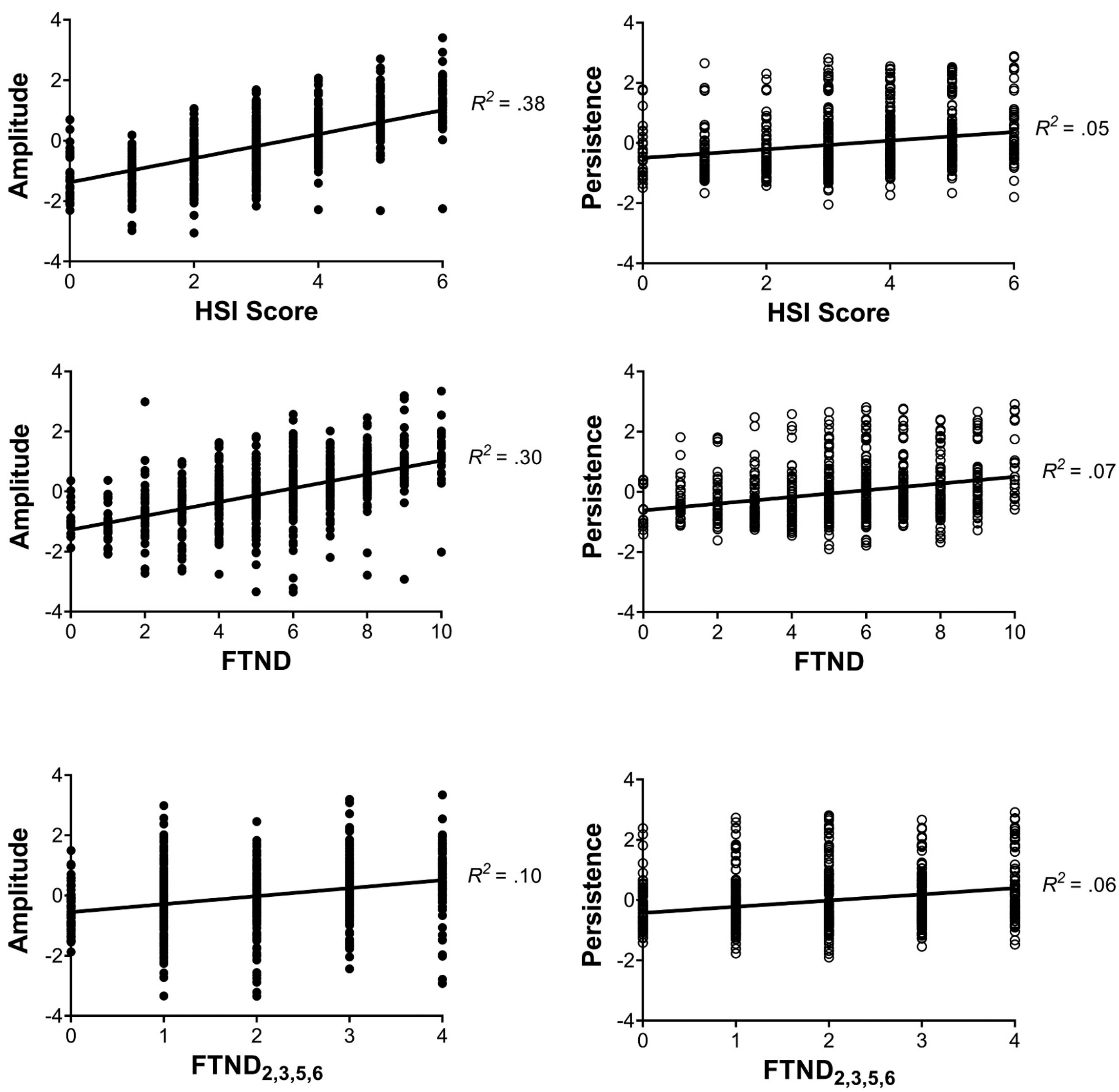

Fig. 2. Shown are best-fit lines for associations between scores on the Cigarette Purchase Task latent factors Amplitude (solid lines) and Persistence (hashed lines) with Heaviness of Smoking (HSI) total scores, Fagerström Test of Nicotine Dependence (FTND) total scores, and Fagerström Test of Nicotine Dependence total scores minus items 1 and 4 ($FTND_{2,3,5,6}$). R2 values represent total variance in factor scores accounted for by increasing dependence-severity scores.

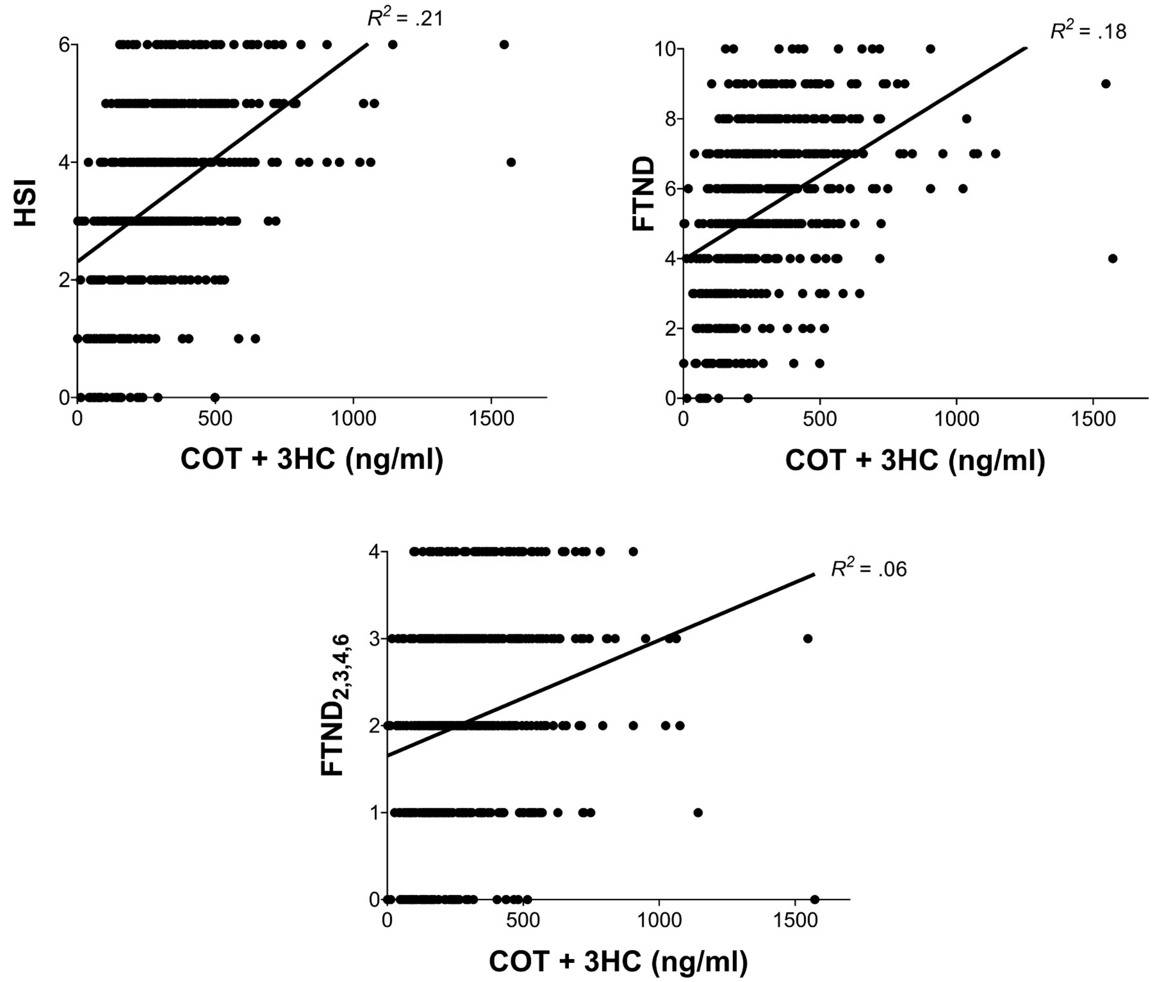

Fig. 3. Shown are best-fit lines for associations between Heaviness of Smoking (HSI) total scores, Fagerström Test of Nicotine Dependence (FTND) total scores, and Fagerström Test of Nicotine Dependence total scores minus items 1 and 4 ($FTND_{2,3,5,6}$) with combined cotinine (COT) and 3′-hydroxycotinine (3-HC) levels (COT + 3-HC ng/ml). R2 values represent total variance in dependence-severity scores accounted for by increasing COT + 3-HC ng/ml levels.

$p < .0001$, $\eta^2 = 0.09$), just slightly less with FTND total scores (F(1, 517) = 55.48, $p < .0001$, $\eta^2 = 0.08$), and least with $FTND_{2,3,5,6}$ total scores (F(1, 517) = 14.37, $p = .0002$, $\eta^2 = 0.02$) (Fig. 3).

In multivariable modeling with CPT factor scores, COT + 3HC (ng/ml) levels were significantly associated with Amplitude (F (1,517) = 22.73, $p < .0001$, $\eta^2 = 0.04$) but not Persistence (F(1, 517) = 1.71, $p = .19$, $\eta^2 < 0.01$) (Fig. 4). We saw no evidence of significant mediation by Persistence in the association of COT + 3HC with Amplitude.

There was no significant association between NMR and HSI total scores (F(1,517) = 1.76, $p = .19$, $\eta^2 = 0.00$), although there were significant associations between NMR and FTND total scores (F

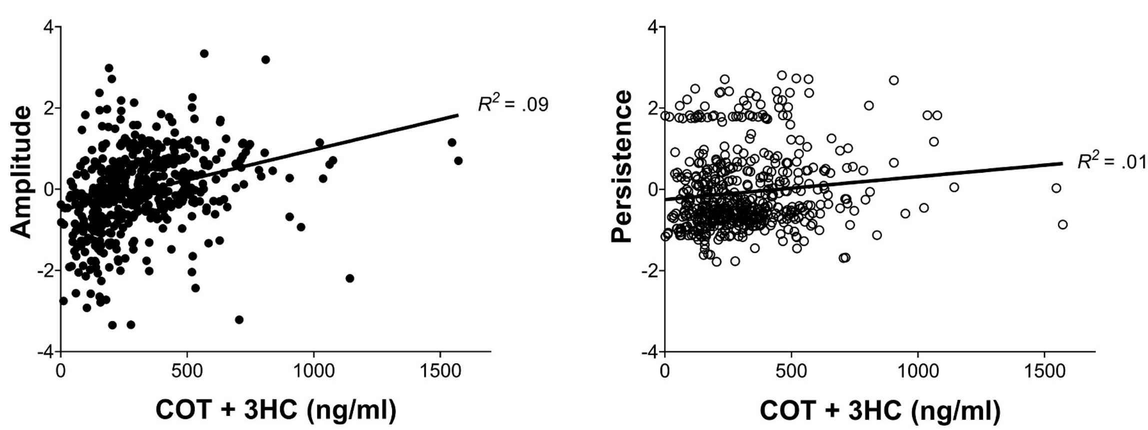

Fig. 4. Shown are best-fit lines for associations between scores on the Cigarette Purchase Task latent factors Amplitude (solid lines) and Persistence (hashed lines) with combined cotinine (COT) and 3′-hydroxycotinine (3-HC) levels (COT + 3-HC ng/ml). R2 values represent total variance in factor scores accounted for by increasing COT + 3-HC ng/ml levels.

$(1,517) = 6.94$, $p = .01$, $\eta^2 = 0.01$) and $FTND_{2,3,5,6}$ total scores ($F(1,517) = 11.40$, $p = .001$, $\eta^2 = 0.02$) with slower metabolizers having greater dependence severity.

NMR was not significantly associated with Amplitude ($F(1, 517) = 0.28$, $p = .60$, $\eta^2 < 0.01$) or Persistence ($F(1, 517) = 0.18$, $p = .67$, $\eta^2 < 0.01$).

4. Discussion

The present results further demonstrate the utility of the CPT for providing a detailed, quantitative characterization of the relative reinforcing value of smoking (i.e., smoking motivation) (Gonzalez-Roz et al., 2019; Reed et al., 2020; Zvorsky et al., 2019). Consistent with prior studies in adolescent (Bidwell et al., 2012) and adult smokers (Gonzalez-Roz et al., 2020; O'Connor et al., 2016), the five conventional CPT indices reduced to two latent factors. Those two factors accounted for 80% of the variance in the intercorrelational matrix of the indices, which is consistent with values observed in the prior studies with adolescent and adult smokers. The Intensity index which was of particular interest in the present study loaded exclusively onto Amplitude without any other index doing so. That was also the case in the prior studies with adult smokers (Gonzalez-Roz et al., 2020; O'Connor et al., 2016) while among adolescents O_{max} also loaded onto Amplitude (Bidwell et al., 2012). Each of the indices other than Intensity loaded onto Persistence in the present and prior studies. Considered together the results demonstrate that the two-factor solution has generality across a broad range of smokers.

Results on associations between dependence severity and CPT factor scores support our hypothesis that associations would be stronger for Amplitude (unconstrained demand) than Persistence (price sensitivity). That pattern was consistent across the three dependence measures, but especially HSI and FTND total scores, each of which included the two FTND consumption items. The FTND was included in bivariate analyses in the prior studies examining CPT latent factors in adolescents (Bidwell et al., 2012) and adult lighter smokers (O'Connor et al., 2016). At least two patterns are notable when comparing results across the present and those prior studies. First, dependence severity had almost identical levels of association with Amplitude and Persistence among adolescents ($r = 0.21$ and 0.22, respectively) but not lighter adult smokers ($r = 0.29$ and 0.11, respectively) nor the heavier adult smokers in the present study ($r = 0.62$ and 0.22, respectively). Second, while the strength of the association between dependence severity and demand Amplitude increases when looking across studies in adolescent, adult lighter, and adult heavier smokers (r = 0.21, 0.29, 0.62, respectively), no such trend is discernible for Persistence ($r = 0.22$, 0.11, and 0.22, respectively). These patterns suggest that while both factors are associated with dependence risk, the former more than the latter represents the dominant motivational process underpinning dependence severity in established, adult smokers, especially heavier smokers, and that this pattern appears to develop over the life-course of chronic smoking.

The present results may provide insight into why the two-item HSI better predicts cessation outcomes than the full FTND or $FTND_{2,3,5,6}$ (Baker et al., 2007; Fagerström et al., 2012). While the FTND includes the same two consumption items as the HSI, the total score represents the other FTND items as well and ends up having a somewhat weaker association with demand Amplitude and only slightly stronger association with demand Persistence. The same applies to the $FTND_{2,3,5,6,}$ which totally excludes the two consumption items. If demand Amplitude is the more important contributor than Persistence to cessation difficulties, that alteration may be sufficient to weaken the relative predictive utility of the FTND and $FTND_{2,3,5,6}$ compared to the HSI. That possibility would seem to be bolstered by the observation that demand Amplitude is significantly associated with total nicotine intake while demand Persistence is not.

We saw no evidence that NMR has any relationship with individual differences in CPT factor scores. We know of no prior studies on this topic against which to compare these results. It seems plausible that the psychiatric and socioeconomic vulnerabilities around which the present study sample was recruited may have sufficiently strong associations with heavy smoking to obscure any NMR influence. That same explanation might also apply to the absence of a significant association between NMR and HSI scores. We are more puzzled by the inverse association between NMR and FTND and $FTND_{2,3,5,6}$ scores, although as noted above associations between NMR and FTND scores are known to vary considerably depending on sex, race, and perhaps other participant characteristics (Schnoll et al., 2014).

In terms of informing development of more effective interventions to reduce smoking in vulnerable populations, these results suggest potential benefit from greater targeting of demand Intensity or Amplitude. Unfortunately, the CPT has been included in only a modest amount of intervention research and all examined CPT demand indices rather than factor scores. The CPT has been included in at least three studies where reducing the nicotine content of cigarettes decreased CPT demand Intensity (Higgins et al., 2017; Higgins et al., 2020; Smith et al., 2016). Moreover, 6–12 weeks of using reduced nicotine content cigarettes decreased demand Intensity for the research cigarettes as well as participant usual-brand cigarettes (Higgins et al., 2020; Smith et al., 2016). We know of two relevant studies examining psychosocial interventions. One was a smoking-cessation trial wherein greater baseline demand Intensity and lower demand Elasticity predicted poorer outcomes in the control condition but not the intervention condition where participants received vouchers contingent on abstaining from smoking (i.e., the abstinence-contingent incentives ameliorated the disruptive effects of baseline demand on cessation) (MacKillop et al., 2016). The other study demonstrated that Episodic Future Thinking (developing and reviewing vivid imagery of positive future events) decreases demand Intensity as well as delay discounting (Stein et al., 2018). We are aware of three controlled smoking-cessation trials examining the effects of pharmacotherapies on CPT indices, bupropion (Madden and Kalman, 2010), varenicline (Murphy et al., 2017; Schlienz et al., 2014), and transdermal nicotine (Murphy et al., 2017). None reduced demand intensity or other CPT indices. These trials were more preliminary, proof-of-concept than well-powered cessation trials (e.g., samples sizes ranged from 60 to 110). Thus the negative findings should be interpreted cautiously pending further examination in larger trials.

The present study has several limitations that merit mention. Because participants represent a convenience rather than a nationally representative sample, results may not generalize to other smokers with these same vulnerabilities. Additionally, inclusion was limited to daily smokers and those who not regularly use other tobacco products, which could limit generality of the results to growing subgroups of non-daily smokers and users of e-cigarettes and other tobacco products (e.g., Weinberger et al., 2018). Lastly, women were overrepresented in the sample due to one of the vulnerable populations being exclusively female. Sex was included as a covariate in all analyses, but nevertheless we cannot rule out that results may be more representative of smoking motivation and dependence severity among women than men.

Those limitations notwithstanding, this study provides new knowledge relating individual differences in dependence severity across the HSI, FTND, and $FTND_{2,3,5,6}$ to underpinning motivational and pharmacological processes. All three dependence measures were associated with CPT factors scores, with those associations generally being stronger for demand Amplitude than Persistence, especially with the HSI and FTND. Indeed, the relatively stronger and exclusive association of HSI total scores with demand Amplitude compared to the FTND and $FTND_{2,3,5,6}$ total scores may account at least in part for why the HSI is a better predictor of cessation outcomes. That possibility is bolstered by the observations that demand Amplitude but not Persistence is associated with total nicotine intake levels. Those observations, along with between-study results suggesting that the relationship between dependence severity and demand Amplitude becomes progressively stronger across adolescent, adult lighter, and adult heavier smokers, suggests that demand Amplitude may be a useful intervention target in efforts to improve reduce smoking especially in more treatment recalcitrant or vulnerable populations. We saw modest associations between NMR and dependence severity as measured by the FTND and $FTND_{2,3,5,6}$ and none with the HSI or either CPT Amplitude or Persistence suggesting a negligible impact of that pharmacological process on the relative reinforcing value of smoking in vulnerable populations.

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