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Refining the Tobacco Dependence Phenotype Using the Wisconsin Inventory of Smoking Dependence Motives: II. Evidence from a Laboratory Self-Administration Assay

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Abstract

Prior analyses of the Wisconsin Inventory of Smoking Dependence Motives implicated four subscales as “Primary Dependence Motives” (PDM) indexing the core features of tobacco dependence, with the remaining subscales reflecting “Secondary Dependence Motives” (SDM; Piper, Bolt, Kim, Japuntich, Smith, Niedereppe, Cannon & Baker, 2008). The current study extended this work by examining the correlates of PDM, SDM, their subscales, and other indicators of dependence in an operant self-administration paradigm. Smokers (N=58) worked for cigarette puffs under differing fixed ratio schedules. Analyses focused on predicting self-administration under conditions of minimal constraint on tobacco access, and on withdrawal and craving under conditions of severe constraint. Results support a two-factor model of dependence, with the PDM factor showing relatively stronger relations with tobacco self-administration, and SDM showing relatively stronger relations with withdrawal symptomatology and distress-related craving. The PDM appears to index core features of tobacco dependence, but susceptibility to deprivation-contingent distress and craving may be better indexed by SDM.

Keywords

smoking; tobacco dependence; motives; self-administration; craving

Historically, tobacco dependence has been measured using assessments such as self-reported cigarettes per day, the DSM-IV diagnostic criteria, or the Fagerström scales (for a review, see Piper, McCarthy & Baker, 2006). These indices assess broad endpoints or surface features of tobacco dependence, such as heavy smoking or difficulty quitting. More recently, investigators have introduced theoretically derived multifactorial scales with the aim of capturing individual differences in an array of specific, narrower facets of dependence (e.g., Piper, et al., 2004; Shiffman, Waters, & Hickcox, 2004). These instruments offer the potential to “bootstrap” toward a more sophisticated understanding of the tobacco dependence construct (e.g., Cronbach & Meehl, 1955).

The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68, Piper, et al., 2004) is a multifactorial dependence questionnaire comprising 68 items organized into 13 subscales. The WISDM-68 was designed to tap conceptually distinct motivational processes emphasized by prominent theoretical accounts of drug dependence. Table 1 lists the 13 WISDM-68 subscales and describes the content targeted by each.

Piper et al. (2008) used a variety of person- and variable-centered analyses of WISDM-68 data to investigate the nature and structure of tobacco dependence. The guiding notion behind their approach was that tobacco dependence, like other disorders, may consist of *core features* that are necessary and sufficient for diagnosis and *accessory features* that can provide supplementary information about noncentral attributes. This model suggests the existence of a group of smokers who show high levels of the core, but not the accessory features. Latent profile analyses were conducted in four different samples to identify subgroups of smokers with distinct profiles of scores across the WISDM-68 subscales. Results consistently supported a five-class solution. Of these, four profiles differed chiefly along a severity dimension (i.e., the classes differed from one another on the basis of elevation across all scales) but in each sample one group of smokers emerged with a unique profile. This group was characterized by high scores on just four subscales (Loss of Control, Craving, Automaticity, and Tolerance) and relatively low scores on the others. Based on the expectation that some smokers would show only the core features of dependence, Piper et al. (2008) tentatively concluded these four subscales might index the core of tobacco dependence. Exploratory factor analyses and factor-mixture analysis also suggested the WISDM-68 subscales could be organized into two correlated factors, with one factor defined by Loss of Control, Craving, Automaticity, and Tolerance.

Based on the total pattern of evidence, Piper et al (2008) labeled these subscales the “Primary Dependence Motives” (PDMs) and dubbed the remaining nine scales the “Secondary Dependence Motives” (SDMs).

Summary PDM and SDM scores were computed by averaging scores from the relevant subscales. Both summary scores were tested, singly and in combination, as predictors of a variety of dependence-related criteria including smoking rate, Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) and DSM-IV dependence criteria, diary-measured postcessation craving and withdrawal, and relapse to smoking. Results revealed that, while both PDM and SDM scores were univariate predictors of these criterion measures, PDM scores were generally stronger predictors and tended to eclipse SDM scores when both were entered simultaneously in regression analyses. A notable exception was that SDM emerged as a better predictor of quit day craving than the PDM, despite the inclusion of the Craving subscale in the PDM score.

Identifying the core features of dependence is necessary to distill the most promising phenotype(s) for molecular genetics research on tobacco dependence (e.g., Baker, Conti, Moffitt, & Caspi, 2009). The distinction between PDM and SDM phenotypes has already received support in such research. Using data from three samples of smokers, Weiss, et al. (2008) found strong associations between *CHRNA5-A3-B4* haplotypes and tobacco dependence as defined by high FTND scores among those starting daily smoking prior to age 17 (early-onset smokers). Four common haplotypes (A, B, C, and D) were observed in a SNP discovery survey focused on regions on chromosome 15 related to nicotinic acetylcholine receptors (nAChRs). Smokers who carried Haplotype A were at elevated risk for tobacco dependence as indexed by the FTND (see also Saccone, et al., 2007; Thorgeirsson, et al., 2008). Baker, Weiss, et al. (2009) extended this work by showing that Haplotype A was associated with higher dependence as assessed by both PDM and SDM among early-onset smokers. However, effects for SDM appeared to be attributable to

variance shared between SDM and PDM (zero-order $r = .72$). Haplotype A was also associated with higher risk of relapse. Thus, the pattern of findings suggests the PDM score may distill information about relapse-relevant individual differences related to heritable variations in nAChR subunits. It should be noted, however, that some investigations have failed to observe associations between SNPs in the *CHRNA5-A3-B4* cluster and relapse (Breitling, et al., 2009; Conti, et al., 2008).

While these results are promising, there is a need for further investigation of the correlates of PDM, SDM, and their constituent scales, particularly in light of the genetic association evidence. One limitation of existing evidence is that it does not directly address whether WISDM-68 subscales and composites reflect genuine differences in motivation to smoke rather than biases, quirks, or artifacts of self-report. For example, smokers who inhabit environments with few smoking prohibitions or who have substantial economic resources might smoke heavily (Tolerance) or without forethought (Automaticity) simply because they have the opportunity to develop or display these behaviors in daily life. Thus, statistical associations between PDM and self-reported smoking rate, exhaled carbon monoxide levels, and FTND scores (Piper, et al., 2008) could merely reflect these variations in living conditions rather than meaningful motivational phenomena. This is of critical concern because the ability of a dependence measure to predict tobacco self-administration is a key validity criterion (Piper, et al., 2006). Criterion contamination might also play a role. The major dependence scales all elicit information about smoking heaviness. Therefore, there is considerable overlap between the assessment of the predictor (the dependence scale) and the criterion (self-reported smoking rate), providing a questionable validity test. One way to probe this is to bring smokers into a laboratory and relate dependence scores to an arbitrary measure of nicotine self-administration and other criteria under standardized conditions. If WISDM-68 composites and subscales truly measure motivational processes, they should predict behavior in a standard, novel test context.

The current project examines the correlates of WISDM-68 subscales and PDM and SDM summary scores in an operant self-administration paradigm. Smokers were given access to cigarette puffs under a variety of fixed ratio schedules in separate laboratory sessions. Prior work attests that self-administration under comparable laboratory conditions indexes smoking motivation (e.g., Bickel & Madden, 1999; Madden & Bickel, 1999; Shahan, Bickel, Madden, & Badger, 1999) and that imposing more stringent work requirements to earn tobacco puffs decreases tobacco consumption (Bickel, DeGrandpre, Hughes & Higgins, 1991; Bickel & Madden, 1999; Madden & Bickel, 1999; Shahan, et al., 1999). Therefore, this paradigm presents the opportunity to investigate the relations of WISDM-68 measures with specific self-administration behavior with minimal constraints on use and with deprivation-related phenomena under conditions of significant constraint.

The main goals of this research were threefold. The first goal was to test a particular model of the structure of nicotine dependence in which one component (indexed by PDM) is especially predictive of tobacco self-administration and a second component (indexed by SDM) is especially predictive of abstinence distress. This model is based on (1) the content of the PDM scales and their associations with other measures of tobacco self-administration (e.g., Baker, et al., 2007; Piper, et al., 2008), (2) the fact that heavy use and withdrawal may arise through different genetic mechanisms (cf. Baker, Weiss, et al., 2009; Damaj, Kao & Martin, 2003; Gilbert, Zuo, Rabinovich, Riise, Needham & Huggenvik, 2009; Hardin, et al., 2009; Jackson, Martin, Changeux, & Damaj, 2008), and that these two features are often found to be weakly associated in other research (Baker, Conti, et al., 2009; Piasecki, Fiore, & Baker, 1998; Piper, et al., 2006), and (3) previous research (Piper, et al., 2008) that found that SDM scores were better predictors of craving on the quit day than were PDM scores. A second goal was to compare the magnitude of the predictions yielded by the PDM and SDM

with an alternative dependence index that has been validated in a great deal of previous research (i.e., the FTND) to gauge the relative validities of these newer empirically derived composites. The final goal was to determine how WISDM-68 subscales are related to dependence criteria in an effort to elucidate the nature of the PDM and SDM composites and identify potentially important dependence processes.

Method

Participants

Participants were recruited from the community in Columbia, Missouri via flyers placed on public bulletin boards and kiosks. Inclusion/exclusion criteria were: (a) age 18 years or older, (b) smoke cigarettes at least 4 days per week for the past 6 months, (c) able to read and write English, (d) not trying to quit smoking or using nicotine replacement or other smoking cessation pharmacotherapy, and (e) not using tobacco products other than cigarettes. Participants were paid \$10 per hour, and completion of the study took approximately 13 hours over 5 separate visits.

A total of 58 participants (34 male, 24 female) completed all sessions and completed the dependence questionnaires. The analyzed sample contained substantial variability in smoking behavior and dependence levels. The mean self-reported smoking rate was 17.2 cigarettes per day ($SD=9.5$; range 3 – 50; $Mdn=15$), the mean score on the FTND was 4.0 ($SD=2.5$, range: 0–10) and the mean score on the WISDM-68 was 58.6 ($SD=14.6$, range: 23.8 – 88.7).

Project Background and Data Selection

The current analyses focus on data collected during two operant sessions. These data were collected as part of a larger design in which each participant completed four operant sessions. In a given session, a participant was able to earn cigarette puffs under a fixed ratio (FR) schedule requiring 50, 250, 750, or 1500 computer mouse clicks per puff. Each participant completed one session under each schedule. The original goal was to fit behavioral economic demand curves to puff consumption data for each participant (Hursh, Raslear, Shurtleff, Bauman & Simmons, 1988). Conceptually, fitted curve parameters might index individual differences in both heaviness of consumption under minimal constraints and defense of habitual intake in the face of rising constraints. In the aggregate, mean puff consumption was well-predicted by the Hursh equation ($R^2 = .99$). However, at the individual level, demand curves frequently fit poorly,¹ leading us to conclude the obtained curve parameters were not suitable for use as dependence measures.

Clearly, however, the data from constituent sessions have value and are interpretable outside the intended economic analysis. In light of the Piper et al (2008) findings, we revisited these data to investigate the how WISDM-68 PDM and SDM composites were related to tobacco self-administration and symptoms of tobacco deprivation. We focused the current analyses on predicting self-administration during the FR 50 session, when constraints were minimal and predicting abstinence symptoms at the end of the FR 1500 session, when constraints on tobacco access were severe and abstinence effects were most pronounced. We selected these data points as the most informative on a priori conceptual grounds, and a variety of supplementary analyses supported this approach.²

¹For example, some participants consumed more puffs at a higher price than at a lower price, creating a curve resembling a “dish” rather than a “hump.” Inadequate resolution at the low end of the price continuum also led to inflated intercept estimates in some cases. These issues likely reflect defects in the specific procedures used; more reliable curves might be obtained using additional sessions, longer sessions, or a different set of prices. However, if indifference to tobacco is characteristic of the *absence* of dependence, then operant assessment may be feasible only among heavier, more dependent smokers likely to show orderly demand.

Procedure

Baseline session—Each participant reported to the laboratory for a brief baseline session in which self-report questionnaires were administered and the experimenter provided training in the operant task, cigarette lighting procedure, and the puffing protocol that would be used in operant sessions. Participants smoked a cigarette during this training, and a breath carbon monoxide (CO) reading was collected when the cigarette was extinguished. Participants were instructed that they should abstain from smoking for at least 2.5 hours prior to each of the remaining sessions and that this would be confirmed by CO.

Operant sessions—Operant sessions were scheduled at the participants' convenience with the constraints that they start at approximately the same time of day (e.g., within one hour) and that they all be held within a 14-day period. Operant sessions were held in a 10×16 room adjacent to a control room. Upon arrival, participants provided a CO sample and were required to obtain a reading of 75% or less compared to the post-smoking reading in the baseline session. If participants did not meet this criterion, they were either rescheduled or allowed to wait until they reached the threshold to begin the session³. Participants were seated at a desk in front of two computers, one of which controlled the operant task, and the other was linked to a puff topography device (CReSS, Plowshare Technologies, Baltimore, MD). At the outset of the session, participants completed questionnaires and were then permitted a “free” 40ml puff to equate them on the time since last smoking.

Experimenters told participants the work requirement to earn puffs in the session. The order of the FR 50, FR 250, and FR 750 sessions was counterbalanced across participants. The FR 1500 price was always used in the last session because participants were asked to smoke an ad lib cigarette at the end of the FR 1500 session; we were concerned experiencing a “free” cigarette might produce carryover effects if there were subsequent sessions (e.g., DeGrandpre, Bickel, Rizvi, & Hughes, 1993). Participants were told they could smoke as many or as few puffs as desired over the next three hours, but that they must earn any puffs they took by making the required number of mouse clicks. Participants were told that if they earned a puff, they must take it immediately (i.e., puffs could not be “saved up”). When not working for puffs, participants could read or listen to a radio. At this point, the experimenter left the room and monitored the participant via closed-circuit television to make sure participants were not taking extra puffs, sleeping, talking on mobile phones, and so on.

When a participant made enough mouse clicks to earn a puff, the computer program running the operant task reset the click tally on the display to zero and cued the participant to take a puff according to a standardized puffing procedure. To avoid unearned inhalation of the

²We considered predicting self-administration under minimal constraints (FR 50) and the change in self-administration with increasing constraints. However, change in number of puffs consumed from the lowest to the highest FR session was essentially redundant with level of smoking in the FR 50 session ($r = .96$) because very little smoking occurred in the FR 1500 session. Mixed models using puff data from all sessions as the dependent measure and including session as repeated factor revealed robust and consistent interactions between session and various dependence scales. Those higher in dependence showed steeper decreases in consumption with increased FR, a finding that is inconsistent with the notion that greater dependence would be associated with inelastic demand or defense of habitual intake. An alternative interpretation of the effects is that prediction of self-administration from dependence scales was strongest at FR 50, and we interpreted the interactions as reflecting metric factors (e.g., law of initial values, restriction of range). Interactions between scales and session were also found when predicting withdrawal and craving, but in these models, the strongest scale effects were seen in the FR 1500 session. In short, we believe the interactions reveal that the individual sessions differed with respect to their quality as dependence-related criteria, and the reported analyses focus on data from the most informative or diagnostic sessions. Because of the interaction effects, models using data from all sessions produced a more complicated set of findings. However, the substantive pattern of findings (e.g., relative associations between specific dependence measures with laboratory criteria) was very similar to the results of the simpler analyses reported here.

³Due to scheduling constraints, three participants (one in an FR 50 session and two in FR 1500 sessions) were permitted to begin the session without meeting the desired CO threshold. In all cases, the observed CO reading was lower than the value recorded at screening (81%, 81%, and 93%). Omitting these subjects from the analyses changed the findings very little.

lighting puff, participants were trained to light cigarettes by using a turkey baster. Cigarette puffs were smoked using the CReSS puff transducer and directed smoking module. Earned puffs were 60 ml in volume and held for 5 seconds before exhalation. Participants were encouraged to extinguish the cigarette gently and save it for the next puff, but could switch to a fresh cigarette at any time. The investigators furnished a supply of the participant's preferred cigarette brand and style of cigarette for use during the sessions.

After three hours had elapsed, the experimenter administered additional questionnaires. At the end of the FR 1500 session only, the experimenter asked participants to smoke an entire cigarette ad lib. When the participant finished the ad lib cigarette, additional questionnaires were administered, and the participant was dismissed.

Measures

Questionnaire measures—The FTND (Heatherton, et al., 1991) and the WISDM-68 (Piper, et al, 2004) were administered at the baseline session. Internal consistency was acceptable for the FTND ($\alpha = .73$) and the WISDM-68 subscales ($\alpha = .75$ to $.96$). We computed a “Primary Dependence Motive” (PDM) score by averaging scores across the four primary scales and a “Secondary Dependence Motive” (SDM) score by averaging across the nine secondary scales. Internal consistency was high for both (PDM $\alpha = .93$, 18 items; SDM $\alpha = .96$, 50 items).

A modified Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) was administered at the baseline session, the beginning and the end of the operant sessions, and after smoking the ad lib cigarette in the FR 1500 session. The MNWS was administered by computer and assessed the following symptoms on 100-point visual analog scales: urge to smoke, irritability, anxiety, difficulty concentrating, restlessness, hunger, impatience, craving a cigarette, insomnia, increased eating, drowsiness, depression, and desire for sweets. For the current analyses, the “craving” and “urge” items were omitted from the scoring to isolate non-craving withdrawal effects⁴. Internal consistency of the remaining items was high across all administrations (all $\alpha \geq .83$).

The Questionnaire on Smoking Urges (QSU; Tiffany & Drobes, 1991) was administered at the beginning and end of each operant session and after smoking the ad lib cigarette. All QSU items used Likert scales ranging from 0 to 6. The QSU is composed of two correlated factors. Factor 1 comprises 15 items and taps present desire to smoke and anticipation of pleasure from smoking. Factor 2 comprises 11 items and taps expectations for negative reinforcement from smoking, i.e., relief of distressing symptoms. Each QSU subscale demonstrated high internal consistency across administrations (all $\alpha \geq .93$).

Statistical Analyses

Manipulation checks—A series of paired-samples t-tests evaluated whether study procedures were effective in manipulating smoking behavior and motivation in the FR 50 and FR 1500 sessions. These analyses evaluated (a) whether work requirements affected puff consumption, (b) whether participants started sessions in a state of deprivation, (c) whether there was intra-session change in withdrawal and craving, and (d) whether withdrawal and craving were affected by smoking the ad-lib cigarette at the end of the FR 1500 session.

Prediction of self-administration, withdrawal, and craving—We sought to explore the construct validity of the PDM and SDM summary scores and individual WISDM-68

⁴Results were similar when the craving items were included in the MNWS scoring.

subscales for predicting self-administration and subjective reactions to tobacco deprivation in a standardized context. We conducted parallel analyses using the FTND as a predictor to serve as a benchmark. The FTND and PDM both index the important dimension of smoking heaviness, although both measures are intended to assess more than smoking heaviness per se. We therefore conducted additional analyses including CPD as a covariate to evaluate whether the dependence scales added anything unique to the prediction of self-administration, craving, or withdrawal beyond effects associated with CPD. Dependent measures were puff consumption in FR 50 session and MNWS and QSU Factor 1 and 2 as measured at the end of FR 1500 session. For each outcome, we performed a set of regression analyses with a single dependence indicator (PDM or SDM composite, FTND, or WISDM-68 subscale) as the predictor. Next, we retested each predictor after covarying CPD to evaluate incremental validity of the scales.

Following Piper et al. (2008), we estimated models in which both PDM and SDM were entered simultaneously as predictors of each criterion measure. This research showed that the discriminative validities of the two composites became more apparent with simultaneous entry. In cases where PDM or SDM emerged as significant predictors, we performed follow-up analyses to explore which individual subscales best accounted for the effect of the composite measure. To investigate overlap and uniqueness of the WISDM-68 composites relative to conventional dependence assessment, we performed an additional set of models in which PDM, SDM, and FTND were entered simultaneously.

Results

Manipulation Checks

Participants consumed more puffs during the FR 50 session ($M = 14.05$, $SD = 8.83$, range = 0–33) than the FR 1500 session ($M = 2.94$, $SD = 2.77$, range = 0–9), $t(57) = 11.30$, $p < .001$. Table 2 gives means and standard deviations for measures of withdrawal and craving at various measurement occasions. Compared to the baseline session, participants scored significantly higher on the MNWS at the beginning of the FR 50 session, $t(57) = 6.05$, $p < .001$ and the beginning of the FR 1500 session, $t(57) = 4.59$, $p < .001$. MNWS scores were unchanged from the beginning to the end of the FR 50 session, $t(57) = 0.67$, $p = .51$, but increased significantly during the FR 1500 session, $t(57) = 2.03$, $p < .05$. Scores on QSU Factor 1 decreased from the beginning to the end of the FR 50 session, $t(57) = 3.47$, $p < .001$, but did not change significantly across the FR 1500 session $t(57) = 1.90$, $p = .06$. Similarly, QSU Factor 2 scores decreased during the FR 50 session, $t(57) = 3.38$, $p < .001$ but were unchanged during the FR 1500 session, $t(57) = 0.72$, $p = .48$. Smoking the ad lib cigarette following the FR 1500 session significantly reduced scores on the MNWS, $t(57) = 6.20$, $p < .001$, QSU Factor 1, $t(57) = 10.95$, $p < .001$, and QSU Factor 2, $t(57) = 8.84$, $p < .001$. In sum, participants arrived at the laboratory in a state of mild tobacco deprivation and withdrawal symptoms increased significantly only during the session where tobacco access was highly constrained (i.e., FR 1500). In addition, craving scores on QSU Factors 1 and 2 decreased significantly only when there were minimal constraints on tobacco access (i.e., FR 50). Smoking an ad lib cigarette at the end of the FR 1500 session reduced withdrawal and craving, further suggesting the effects measured prior to smoking were genuine symptomatic reactions to tobacco deprivation.

Intercorrelations Among Predictors

Table 3 provides the zero-order correlations among all of the variables used as predictors of self-administration and subjective states. All of the correlation coefficients were positive, and most were statistically significant. It is noteworthy that the PDM score was more robustly related to both CPD and the FTND ($r_s = .65$ and $.71$, respectively) than was the

SDM score ($r_s = .40$ and $.38$, respectively), despite the fact that the PDM and SDM scores were themselves strongly intercorrelated ($r = .72$). Formal tests of the differences between correlations (Cohen & Cohen, 1983) indicated that the PDM correlation was significantly stronger than the SDM correlation in predicting CPD, $t(55) = 3.27, p < .001$, and FTND, $t(55) = 4.79, p < .001$. This pattern of associations is consistent with evidence from other studies (Piper, et al., 2008) suggesting that the PDM and SDM scores represent correlated factors, but that the PDM is more specifically related to heavy use. All the PDM subscales were significantly related with CPD and the FTND, which was not the case for the SDM subscales.

Prediction of Self-Administration, Withdrawal, and Craving

Table 4 provides standardized regression coefficients from models predicting puff consumption and subjective states from individual dependence scales when either entered alone or after covarying self-reported CPD. When CPD was considered as the sole predictor, it was significantly associated with puff consumption ($\beta = .58, p < .001$) and both craving measures (QSU Factor 1: $\beta = .29, p < .05$; QSU Factor 2: $\beta = .28, p < .05$). CPD was modestly related to withdrawal ($\beta = .23, p = .08$).

The PDM score, each PDM subscale, the SDM score, 3 SDM subscales (Affiliative Attachment, Behavioral Choice/Melioration, and Cognitive Enhancement) and the FTND score each predicted puff consumption in the FR 50 session when entered alone. After covarying CPD, only the PDM total score, Automaticity, Tolerance, and the FTND provided incremental prediction of self-administration when each was entered as an individual predictor.

All of the tested predictors except Tolerance and Social/Environmental Goads were associated with withdrawal scores at the end of the FR 1500 session when entered alone. When CPD was covaried, Taste/Sensory Properties, and FTND were no longer significantly associated with withdrawal.

Significant univariate predictors of QSU Factor 1 scores at the end of the FR 1500 session included the PDM score and each of the PDM subscales, the SDM score, Affiliative Attachment, Behavioral Choice/Melioration, Cue Exposure/Associative Processes, Taste/Sensory Properties, and the FTND. After covarying CPD, only the PDM score, Craving, Cue Exposure/Associative Processes and Taste/Sensory Properties remained significant.

All predictors were significantly associated with QSU Factor 2 scores at the end of the FR 1500 session when tested alone. After controlling for CPD, all predictors except for Weight Control and the FTND remained significant.

Relative Magnitudes of Prediction—The top portion of Table 5 presents estimated beta coefficients from regression analyses predicting each outcome in multivariate analyses in which PDM and SDM were entered simultaneously. The PDM score significantly predicted self-administration. The SDM score predicted puffs as well, though the direction of the effect was negative. The PDM score significantly predicted QSU Factor 1 scores. The SDM score was a unique predictor of MNWS and QSU Factor 2 scores. When the FTND was included in these models, it was not a significant predictor in any model -- PDM remained significantly related to self-administration, but no longer predicted QSU Factor 1 and SDM remained a significant predictor of withdrawal and QSU Factor 2 (Table 5).

Follow-up analyses were performed to identify which subscales might account for the PDM effect for puff consumption and QSU Factor 1 and SDM effects for MNWS and QSU Factor 2. In these models, the nonsignificant WISDM-68 composite (i.e., PDM or SDM) was

forced in at the first step. The significant WISDM-68 composite was omitted. At a second step, all subscales comprised by the omitted composite were tested using stepwise entry to identify the most important subscales. Results from these models are given in the bottom portion of Table 5. For puff consumption and QSU Factor 1 scores, the SDM score was forced into the model. Of the PDM scales, Automaticity and Tolerance were both selected at the second step in the model predicting puff consumption. In the model predicting QSU Factor 1 scores, the Craving subscale was the only measure selected at the second step. For both MNWS and QSU Factor 2, the PDM scores was forced in to the model at the first step. Of the SDM scales, the Cue Exposure/Associative Processes subscale was selected at the second step in both models. Weight Control was selected as an additional predictor in the model predicting MNWS scores. In the model predicting QSU Factor 2, the PDM composite was also significant. Additional exploratory analyses (not tabled) suggested that, as would be expected from findings in Table 4 and scale contents, the Craving subscale best accounted for this residual association of PDM and QSU Factor 2.

Discussion

The Structure of Dependence

The goal of this research was to use data on self-administration and deprivation-related distress from a controlled laboratory experiment to provide further insight into the nature and structure of tobacco dependence. Prior research showed that the PDM subscales and the SDM subscales reflect distinct factors and that this two-factor structure has good model fit in variable-centered analyses. Moreover, person-centered analyses showed that differential scoring on the two composites characterizes a distinct latent class. Those results suggested that the PDM subscales tap core, necessary components of dependence while the SDM subscales tap auxiliary motives. PDM has shown stronger associations with smoking heaviness and relapse criteria, while SDM has shown stronger associations with tobacco abstinence effects. These two factors were differentially related to genetic correlates of dependence such that the PDM had stronger relations than did SDM with a key chromosome 15 nAChR haplotype that is strongly associated with smoking heaviness and perhaps relapse vulnerability (cf. Baker, Weiss, et al., 2009; Breitling, et al., 2009; Conti, et al, 2008).

The current research was intended to relate the PDM and SDM with measures of tobacco motivation that were gathered in a novel, controlled, assessment context, indexed with an arbitrary self-administration response. In theory, this would provide a strong tests of internal motivation that is relatively unaffected by criterion contamination and other biases (e.g., smoking restrictions, lifestyle factors). Consistent with the previous self-report research, PDM subscales were more highly related to both measures of smoking heaviness (CPD and FTND, see Table 3) and operant self-administration than were the SDM subscales. In fact, the PDM continued to predict earned puffs when CPD was entered into the regression model, while SDM did not (Table 4). When both PDM and SDM were jointly entered into the regression models, the former was significantly positively related to puffs, while the latter was significantly negatively related (Table 5)⁵. As in past research (Piper et al., 2008), the correlations of PDM and SDM with self-administration and withdrawal, respectively, became more highly differentiated or divergent when both were simultaneously entered into

⁵A suppression effect was noted when PDM and SDM were simultaneously entered into the prediction model for puffs earned (Table 5), i.e., residualized PDM was significantly positively related while residualized SDM was negatively related. In simple terms, if two individuals differed on SDM score but not on PDM, the one with the *lower* SDM score would tend to earn more puffs. This finding could be due to collinearity. However, this finding replicates analogous suppression effects in Piper, et al. (2008). Piper, et al. (2008) speculated that such residual variance in SDM picked out individuals for whom smoking still served instrumental functions and who have not transitioned to severe, core dependence.

prediction models. It is the distilled or orthogonal variance in each that is most specific to the targeted outcomes.

As predicted, the SDM composite tended to be more highly associated with measures related to non-craving withdrawal symptomatology than was the PDM composite. When both PDM and SDM were jointly entered into a regression predicting withdrawal, only the SDM made a significant contribution (Table 5).

With respect to craving, our hypotheses were also supported. QSU Factor 1, which taps craving to smoke right away, was more highly related with PDM than was the SDM. Conversely, SDM was more highly associated than PDM with QSU Factor 2, which taps expectations for negative reinforcement from smoking, i.e., relief of distressing symptoms such as might be occasioned by withdrawal. When both composites were entered simultaneously, only PDM significantly predicted Factor 1 and only SDM predicted Factor 2 (Table 5). Again, this pattern is consistent with the notion that residual variance in the two WISDM-68 composites clarifies the nature of the constructs that each taps. Of the PDM subscales, only Craving was related to QSU Factor 1. Of the SDM subscales, only the Cue Exposure/Associative Processes was related significantly to Factor 2. These findings could point to the strong relation between craving and automaticity of self-administration (e.g., Curtin, McCarthy, Piper, & Baker, 2006) on the one hand, and to the associative elicitation of withdrawal signs and symptoms (Kenny, Chen, Kitamura, Markou & Koob, 2006; Zhou, et al., 2009) on the other hand.

This pattern of association supports a “working” two-factor model of tobacco dependence. One factor may represent PDM-like processes (heavy, automatic, irresistible use associated with hedonically neutral or positive cravings) that are associated with a primary *CHRNA5-A3-B4* haplotype. A second (correlated) factor may index deprivation-contingent cravings related to a desire for negative reinforcement and reports of deprivation-contingent withdrawal symptoms. This dimension may be better tapped by SDM scales and could have distinct genetic underpinnings (e.g., Baker, Conti, et al., 2009; Gilbert, et al., 2009; Hardin, et al., 2009; Jackson, et al., 2008).

This two-factor model suggests a weak linkage between how much individuals smoke and the severity of their withdrawal – at least among heavy smokers. For instance, Tolerance, the WISDM-68 subscale that most directly targets smoking heaviness and which had the highest relation with CPD (Table 3) was one of only two dependence measures to not show a significant relation with withdrawal (Table 4). This accords with other evidence that self-administration heaviness and withdrawal severity are poorly related to one another amongst inveterate smokers (Piper, et al., 2006), and it encourages greater exploration into separate causal models for each (Frenois, Cador, Stinus, & Moine, 2002; Hofford, et al., 2009; Nakagawa, et al., 2005).

These findings might reflect, at least in part, somewhat superficial similarities between the subscale contents and the outcomes associated with them. For instance, the PDM subscales tend to comprise questions about smoking rate, and they correlate more strongly than the SDM with this behavioral outcome. The SDM scales tend to comprise items about distress-related symptomatic reactions, and they tend to correlate relatively highly with verbal symptom reports obtained under conditions of deprivation. Of course, this does not invalidate differential associations of subscales with other outcomes involving less predictor-criterion overlap, such as relapse likelihood or haplotype status. Moreover, use of an arbitrary self-administration ritual offers evidence that the link between PDM and nicotine intake is not wholly due to biases such as criterion contamination.

Relative Magnitude of Prediction

A second purpose of this research was to compare the magnitude of the predictions yielded by the PDM and SDM composites with an alternative dependence index that has been validated in a great deal of previous research (the FTND) to assess the relative validity of the WISDM-68 composites. The results showed that, relative to the FTND, the PDM was a modestly better predictor of puffs earned, and the SDM was a considerably better predictor of withdrawal severity (Table 4). Moreover, the FTND suffered a relatively greater loss of predictive validity when CPD was entered into these regressions than did the PDM and SDM, possibly because the FTND comprises a question about cigarettes smoked per day. Importantly, when the PDM, SDM, and FTND were simultaneously entered into a regression model predicting puffs earned, only the PDM was a significant predictor ($\beta=.70$, $p<.001$); the FTND was only weakly related ($\beta=.17$, $n.s.$; Table 5). Similarly, when all three variables were entered into a model predicting withdrawal severity at the end of the FR 1500 session, only the SDM predicted withdrawal ($\beta=.52$, $p<.001$) while the FTND was negligibly related ($\beta = .06$, $n.s.$, Table 5). When the FTND was entered into multivariate models to predict the two QSU urge factors, it did not significantly increment prediction of either factor (Table 5).

The above results suggest that the PDM and SDM performed well relative to a widely-used and well-validated measure of nicotine dependence (especially when entered simultaneously into prediction models). The superior performance of these composites, however, appeared only when they were used to predict theoretically appropriate criteria, that is, when PDM predicted puffs and SDM predicted withdrawal. The PDM had no more orthogonal validity in predicting withdrawal than did the FTND (Table 5), while the SDM had no more orthogonal validity in predicting puffs earned than did the FTND. These comparisons provide further evidence of the existence of two distinct nicotine dependence factors that have relatively discrete or channeled relations with the criteria. The FTND may not have performed as well as the WISDM-68 composites in the above analyses because its factor structure may not parse the two WISDM-68 factors (Piper et al., 2008) as cleanly as the composites. Also, its relatively small number of items may have constrained reliability or the comprehensiveness of construct assessment. The relative performance of the WISDM-68 composites and the FTND encourages further efforts to distill dependence factors and explore mechanisms that might tie such factors with dependence criteria.

It is somewhat remarkable that the SDM was so strongly related to the withdrawal criterion (Tables 4 & 5). Most evidence suggests that dependence measures have negligible relations with withdrawal measures (Piper, et al., 2006). The current findings of a strong association could be due to several factors. One is that the withdrawal severity criterion was assessed in a standard context and this may have reduced error. Another is that the SDM is a distilled measure (although still quite broad in terms of content) that may target more specifically the dependence-related variance in withdrawal. In any event, the current evidence shows that withdrawal severity can be predicted with meaningful accuracy under favorable circumstances.

WISDM-68 Subscales

A third goal of this research was to investigate how specific WISDM-68 subscales were related to each dependence-relevant criterion. Such information speaks to the validity of the subscales, and may also provide additional insights into the nature of important tobacco dependence processes.

Both Automaticity and Tolerance were significant predictors of self-administration, even after covarying CPD. The Tolerance subscale elicits information regarding smoking

heaviness (Piper, et al., 2004). In this regard, it resembles the FTND (Baker, et al., 2007). The Automaticity subscale, however, taps unique content concerning the existence of a routinized, effortless self-administration sequence. It is notable that both Tolerance and Automaticity were simultaneously significant in a multivariate regression model predicting puff self-administration (Table 5). This suggests one of the reasons for the modest superiority of the PDM composite relative to related phenotypes (CPD, FTND) for predicting puff consumption is that it includes novel content concerning habitual use. The existence of an automatized self-administration action sequence is emphasized as a core feature of drug dependence in several theoretical models (e.g., Curtin, et al., 2006; Newlin & Strubler, 2007; Tiffany, 1990). Interestingly, in the current context a self-reported tendency to engage in “automatic” smoking was significantly predictive of work to earn puffs via a novel and arbitrary self-administration operant. Therefore, responses to this scale may index some core element of dependence that transcends the mere routinization of the act of smoking (e.g., it may reflect motivational factors that foster routinization or mark an advanced or “mature” state of dependence).

The Cue Exposure/Associative Processes subscale emerged as the SDM facet most strongly related to withdrawal and QSU Factor 2. This scale was also one of the only SDM components to predict QSU Factor 1 scores even after CPD was covaried. It is notable that the items on this subscale frequently refer to cue-provoked craving processes (e.g., “There are particular sights and smells that trigger strong urges to smoke.”). The laboratory environment contained specific smoking cues (e.g., cigarettes, ashtray) and was itself a smoking cue (i.e., participants were aware this was a smoking study). This may have fostered the expression of cue-associated craving responses during laboratory sessions.

Cue exposure and associative learning processes are emphasized in many models of drug dependence (e.g., Baker, Piper, Fiore, McCarthy & Majeskie, 2004; Everitt & Robbins, 2005; Newlin & Strubler, 2007; Niaura, et al., 1988). In the current study, the Cue Exposure/Associative Processes subscale was uniquely associated with withdrawal discomfort and negative reinforcement cravings. This may suggest cue-provoked craving, deprivation-contingent dysphoria, and deprivation-contingent cravings arise from overlapping mechanisms indexed by the scale. Of course, it is possible that the Cue Exposure/Associative Processes subscale reflects withdrawal discomfort and cravings for more mundane reasons. For instance, the scale might merely reflect an awareness of, or sensitivity to, internal and external cues.

A comprehensive discussion of subscale-outcome relations is beyond the scope of this article, but we note that some findings supported the construct validity of other subscales. For instance, the Negative Reinforcement subscale was not related to self-administration or QSU Factor 1, but did predict criteria conceptually related to negative reinforcement (e.g., withdrawal and QSU Factor 2). Such evidence supports recent research showing that various WISDM-68 subscales predict theoretically-relevant real-world outcomes as assessed by ecological momentary assessment (Japuntich, Piper, Schlam, Bolt & Baker, 2009), attesting to the construct validity of these subscales.

Limitations

Several limitations should be acknowledged. The sample size was small, potentially affecting the precision or generalizability of effect size estimates. We focused on a subset of data from the larger, original project. We manipulated the work requirement for cigarette puffs, not deprivation per se. Therefore, a trade-off or titration process affects the dependent measures examined here, viz., motivated smokers could work harder to earn puffs if they sought to ameliorate abstinence effects or craving. Investigations using manipulations permitting less latitude with respect to self-administration might obtain stronger or more

uniform abstinence and craving effects with different correlates. In considering the meaning of the findings, we have focused on the strongest or marginal effects, but it is clear that there is a positive correlation manifold among all the dependence indicators (Table 3). In practice, this means most of the dependence indicators will be related to the same criteria, and identifying the best predictors will often require multivariate or mediational strategies pitting individual scales against one another (e.g., Baker, Weiss, et al, 2009). It is possible that some of the variation in predictor-criterion relations could be attributable to unmeasured third variables, differences in metric properties of the predictors, or Type I errors. Finally, the two-factor working model of tobacco dependence we have sketched is bounded by the contents of the WISDM-68 and may not be exhaustive.

Conclusion

The current findings corroborated the value of distinguishing between the PDM and SDM domains and extend our knowledge of their correlates. The findings demonstrated that PDM is relatively strongly associated with self-administration in a novel, controlled environment, and can also predict subjective reactions to constraints on tobacco access. PDM, CPD, and FTND represent overlapping measures, but PDM predicted all outcomes, even when CPD was covaried. PDM also improved prediction of self-administration when entered alongside the FTND. Although PDM appears to be a strong index of core features of dependence, the SDM composite emerged as a better predictor of negative reinforcement craving and withdrawal when entered simultaneously with PDM. This pattern of findings, combined with evidence from other studies, suggests that clinically significant tobacco dependence may consist of at least two correlated dimensions: one defined by heavy, automatic use with craving and one defined by deprivation-contingent subjective distress and craving related to negative reinforcement and/or environmental cues.

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Table 1

Contents of the WISDM-68 Subscales

Composite and Subscale	Target Construct
<i>Primary Dependence Motives</i>	
Automaticity	Smoking without awareness or intention
Craving	Smoking in response to craving or experiencing intense or frequent urges to smoke
Loss of Control	The smoker believes he or she has lost volitional control over smoking
Tolerance	Need to smoke increasing amounts over time to experience the desired effects or the ability to smoke large amounts without acute toxicity
<i>Secondary Dependence Motives</i>	
Affiliative Attachment	A strong emotional attachment to smoking and cigarettes
Behavioral Choice/Melioration	Smoking despite constraints on smoking or negative consequences and/or the lack of other options or reinforcers
Cognitive Enhancement	Smoking to improve cognitive functioning
Cue Exposure/Associative Processes	Frequent encounters with nonsocial smoking cues or a strong perceived link between cue exposure and a desire or tendency to smoke
Negative Reinforcement	Tendency or desire to smoke to ameliorate negative internal states
Positive Reinforcement	Desire to smoke to experience a “buzz” or “high” or to enhance an already positive feeling or experience
Social/Environmental Goads	Social stimuli or contexts either model or invite smoking
Taste/Sensory Processes	Desire or tendency to smoke to experience the orosensory/gustatory effects of smoking
Weight Control	Use of cigarettes to control body weight or appetite

Table 2

Means and standard deviations of withdrawal and craving measures by assessment occasion.

Measurement Occasion	Withdrawal M (SD)	QSU Factor 1 M (SD)	QSU Factor 2 M (SD)
Baseline Session	21.66 (16.08)	--	--
Begin FR 50 Session	35.71 (20.42)	4.78 (1.07)	2.85 (1.51)
End FR 50 Session	34.12 (19.43)	4.09 (1.42)	2.25 (1.44)
Begin FR 1500 Session	33.72 (21.32)	4.41 (1.35)	2.86 (1.63)
End FR 1500 Session	37.08 (21.42)	4.76 (1.21)	2.95 (1.61)
Post-Smoke, FR 1500 Session	27.62 (19.35)	2.88 (1.44)	1.79 (1.59)

Note: Items were averaged to express scores in terms of the original scale anchors. MNWS items were rated on 100-point VAS and the QSU items were rated on a scale from 0 (strongly disagree) to 6 (strongly agree). QSU = Questionnaire on Smoking Urges.

Table 3

Intercorrelations among dependence indicators.

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. CPD	--															
2. FTND	.71	--														
3. PDM	.65	.71	--													
4. SDM	.40	.38	.72	--												
5. <i>Loss of Control</i>	.43	.47	.78	.58	--											
6. <i>Craving</i>	.36	.38	.76	.72	.53	--										
7. <i>Automaticity</i>	.57	.57	.85	.61	.55	.52	--									
8. <i>Tolerance</i>	.68	.82	.86	.50	.56	.55	.62	--								
9. Affiliative Attachment	.47	.34	.63	.78	.54	.54	.57	.43	--							
10. Behavioral Choice/Melioration	.48	.51	.76	.87	.64	.70	.63	.56	.77	--						
11. Cognitive Enhancement	.38	.38	.51	.78	.42	.48	.46	.34	.51	.63	--					
12. Cue Exposure/Associative Processes	<u>.19</u>	<u>.18</u>	.54	.76	.35	.70	.43	.36	.46	.55	.50	--				
13. Negative Reinforcement	<u>.17</u>	<u>.22</u>	.58	.89	.49	.73	.40	.38	.64	.75	.75	.66	--			
14. Positive Reinforcement	.30	.39	.65	.92	.59	.67	.51	.44	.67	.78	.71	.60	.90	--		
15. Social/Environmental Goads	.30	<u>.18</u>	.27	.32	<u>.18</u>	<u>.20</u>	.27	<u>.21</u>	.17	<u>.12</u>	<u>.14</u>	.48	<u>.05</u>	<u>.14</u>	--	
16. Taste/Sensory Processes	<u>.20</u>	<u>.12</u>	.37	.68	.36	.44	.29	.27	.53	.63	.36	.51	.53	.63	<u>.25</u>	--
17. Weight Control	<u>.13</u>	<u>.18</u>	<u>.34</u>	.51	<u>.25</u>	<u>.20</u>	.39	<u>.25</u>	.28	.32	.35	.30	.40	.44	<u>.10</u>	<u>.11</u>

Note: The correlations underlined are not significant. Scales listed in italics are those categorized as PDM subscales. CPD = Cigarettes per day, FTND = Fagerstrom Test for Nicotine Dependence, PDM = WISDM-68 Primary Dependence Motives, SDM = WISDM-68 Secondary Dependence Motives

Table 4

Estimated beta coefficients from models predicting puff consumption, withdrawal, and craving from dependence scales, with and without adjustment for cigarettes per day

Predictor	Puffs ^a		Withdrawal ^b		QSU Factor 1 ^b		QSU Factor 2 ^b	
	Scale as Sole Predictor	Scale after CPD covaried	Scale as Sole Predictor	Scale after CPD covaried	Scale as Sole Predictor	Scale after CPD covaried	Scale as Sole Predictor	Scale after CPD covaried
<i>Primary Dependence Motives</i>								
PDM Composite	0.62***	0.42**	0.43***	0.49**	0.41**	0.38*	0.58***	0.70***
Loss of Control	0.36**	0.13	0.42***	0.39**	0.30*	0.21	0.48***	0.44***
Craving	0.34**	0.15	0.48***	0.45***	0.41***	0.35**	0.64***	0.61***
Automaticity	0.61***	0.42***	0.37**	0.36*	0.27*	0.16	0.45***	0.43**
Tolerance	0.62***	0.42**	0.22	0.12	0.37**	0.33	0.41**	0.40*
<i>Secondary Dependence Motives</i>								
SDM Composite	0.29*	0.07	0.56***	0.55***	0.33*	0.25	0.63***	0.61***
Affiliative Attachment	0.29*	0.02	0.45***	0.44**	0.35**	0.28	0.49***	0.45***
Behavioral Choice/Melioration	0.33**	0.08	0.49***	0.49***	0.34**	0.27	0.55***	0.54***
Cognitive Enhancement	0.33*	0.13	0.36**	0.32*	0.04	-0.08	0.37**	0.31*
Cue Exposure/Associative	0.16	0.05	0.48***	0.45***	0.44***	0.40**	0.55***	0.52***
Negative Reinforcement	0.24	0.15	0.45***	0.43***	0.23	0.19	0.54***	0.50***
Positive Reinforcement	0.23	0.07	0.49***	0.46***	0.19	0.12	0.54***	0.50***
Social/Environmental Goads	0.09	-0.09	0.22	0.17	0.25	0.18	0.36**	0.31*
Taste/Sensory Properties	0.10	-0.02	0.29*	0.25	0.42***	0.38**	0.47***	0.43***
Weight Control	0.09	0.02	0.40**	0.38**	-0.02	-0.06	0.28*	0.25
<i>Fagerstrom</i>								
FTND	0.56***	0.31*	0.27*	0.21	0.31*	0.21	0.36**	0.31

* p<.05,

** p<.01,

*** p<.001;

^a Measured in FR 50 session

^b Measured at end of FR 1500 Session

CPD = Cigarettes per day, FTND = Fagerstrom Test for Nicotine Dependence, PDM = WISDM-68 Primary Dependence Motives, SDM = WISDM-68 Secondary Dependence Motives

Table 5

Estimated beta coefficients from multivariate models predicting each outcome.

Predictor	Puffs ^a	Withdrawal ^b	QSU Factor 1 ^b	QSU Factor 2 ^b
<i>Forced Entry of WISDM-68 Composites^c</i>				
PDM	.85***	.07	.36*	.28
SDM	-.32*	.51**	.07	.42**
<i>Forced Entry of Composites and FTND^c</i>				
PDM	.70***	.01	.30	.29
SDM	-.28	.52**	.09	.42**
FTND	.17	.06	.06	-.01
<i>Stepwise Entry of Subscales^d</i>				
PDM	omitted	.18	omitted	0.40**
SDM	-.21	omitted	.06	omitted
Automaticity (PDM)	.47**	--	--	--
Tolerance (PDM)	.43**	--	--	--
Craving (PDM)	--	--	.36*	--
Cue Exposure/Associative (SDM)	--	.31*	--	.34**
Weight Control (SDM)	--	.25*	--	--

*
 $p < .05$ **
 $p < .01$,***
 $p < .001$ ^a Measured in FR 50 session^b Measured at end of FR 1500 Session^c All predictors entered into the model simultaneously^d Significant composite scale omitted and its component subscales subjected to stepwise entry after forced entry of non-significant WISDM-68 composite.

PDM = WISDM-68 Primary Dependence Motives, SDM = WISDM-68 Secondary Dependence Motives