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## Assessment of Pain in Adolescents: Influence of Gender, Smoking Status and Tobacco Abstinence

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### Introduction

Smoking among youth remains a serious public health problem with approximately 5.2% middle-school and 19.5% high-school-aged children smoking cigarettes. Cessation interventions targeted towards youth are important as 88% of adult daily smokers initiate smoking before age 18. (1) Also, adults who begin smoking during adolescence have greater smoking-related morbidity and mortality, including increased risk for chronic pain. (1)

There is a paucity of information examining the relationship between smoking and acute pain-related distress among adolescent smokers. Our current knowledge of the effects of smoking on pain response is limited to studies done with adults and animals, with the preponderance of data focused on chronic pain syndromes. While we currently look to adult data for guidance in examining associations between smoking and pain in adolescent populations, this is insufficient to inform adolescent smoking behaviors and consequences as adolescents have shorter smoking trajectories, different smoking patterns and generally experience acute pain as compared to adults.

Adult smokers have been shown to have increased pain threshold as compared to nonsmokers. (2, 3) However, the data remains inconclusive about the effect of acute nicotine administration on pain, with some studies observing that smoking inhibits pain following acute pain induction, (4) and others observing that chronic exposure to nicotine may increase overall pain threshold. (5) In adults, early studies demonstrated that deprived and sham cigarette smokers experienced reduced tolerance to painful stimulation compared with nonsmokers. (6, 7) Investigations by Pomerleau and colleagues (8, 9) found an increase in pain tolerance in smokers who used nicotine containing products following a deprivation period. Pauli and colleagues reported elevations in pain threshold in smokers may only occur

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when cigarettes are smoked following 12 hours versus 30 minutes of tobacco abstinence. (10) Further, Perkins et al. demonstrated that nicotine may increase pain detection latencies in smokers and nonsmokers. (11)

Although there has been no investigation of pain alterations produced by smoking or tobacco deprivation in adolescents, it has been proposed that frequent, recurrent exposure to nicotine sensitizes pain receptors in the brain, resulting in changes in neuromodulation of sensory information leading to increased pain perception and decreased pain tolerance. (12) Attentional narrowing has also been shown to impact pain perception. (5) Smokers may be primed to have a greater awareness of pain, as nicotine has been shown to restrict attention to salient environmental cues. (13, 14) It is important to establish if alterations in pain tolerance are observed following nicotine deprivation in adolescents, a high-risk population of smokers who have significantly shorter smoking histories and less established smoking patterns than most adult smokers. Such alterations during abstinence may contribute to the perceived benefits of, and enhance the reinforcing value of, cigarettes, thus maintaining smoking behavior.

The adult smoking literature suggests an association between sex and pain tolerance (15) with female smokers reporting significantly lower pain tolerance than male smokers, and both male and female nonsmokers. (16) Jamner and colleagues also demonstrated that the antinociceptive effects of nicotine were specific for adult male smokers. (3) In regards to the interaction between chronicity of smoking and sex, research has shown a possible relationship between the number of pack-years of smoking and perceived persistence of pain in adolescent female smokers. (17) However, there are no studies elucidating the relationship between sex, smoking and pain perception and tolerance in adolescents. This is an important inquiry, as sex differences may impact the need for targeted cessation treatments.

Our goal was to investigate the effects of regular/daily smoking on pain threshold (PTh), pain tolerance (PTo) and pain intensity (PI) by comparing responses on the Cold Pressor Task (CPT) among adolescent smokers and nonsmokers, and to further elucidate sex differences. The CPT is used to measure PTh, when participants first feel pain, PTo, when participants are no longer able to withstand pain, and PI, level of pain, and has been shown to reproduce subjective feelings consistent with those experienced in pain syndromes. (18) We also aimed to investigate the association between tobacco withdrawal and craving and pain during abstinence and the cardiovascular changes that occur in response to pain. We hypothesized that adolescent female smokers would demonstrate lower PTh and PTo and report greater PI at both minimal and 42-hour deprivation as compared to male smokers and nonsmokers and female nonsmokers. We further believed that there would be an inverse relationship between withdrawal & craving and PTo and PTh.

## Methods

### Participants

Non-treatment-seeking healthy adolescent smokers and nonsmokers were recruited via newspaper advertisements and recruitment sessions in local high schools. The study protocol was approved by the Yale School of Medicine Investigation Committee. Included in this

study were 14–18 year-olds meeting criteria for one of the following groups: 1. Smokers-regular use of tobacco products 3–7 days/week for the past six months or 2. Nonsmokers-no tobacco use in the past 6 months, no use of tobacco products 2 days/month in the past year. Excluded were those with lifetime/current psychiatric diagnosis or severe symptomatology (including substance abuse/dependence), positive urine toxicology screen for opiates, marijuana or cocaine, significant medical illness, regular use of psychoactive medications, and pregnancy. Consent was obtained from parents/legal guardians and assent was obtained from participants. Parents were not provided with any information about adolescents' tobacco/drug use or pregnancy status.

## Design

This is a secondary analysis from a study designed to examine tobacco withdrawal among adolescents. (19) Participants completed initial questionnaires, laboratory assessments and brief physical and psychological exams to determine eligibility. All eligible participants completed an outpatient session conducted at the Children's Clinical Research Center at Yale-New Haven Hospital prior to a two-day inpatient session. The outpatient session was conducted between 2 and 6 pm to minimize diurnal differences in endogenous regulators like cortisol. Prior to the outpatient session, participants were asked to smoke normally; breath carbon monoxide (CO) levels and urine cotinine levels were obtained upon arrival. The CPT was conducted 1-hour into the outpatient session, i.e. minimal nicotine deprivation. As inpatients, participants abstained from smoking from admission to discharge (48 hours). Participants engaged in the CPT after a 42-hour deprivation period during which pain ratings, blood pressure, heart rate and salivary cortisol were measured.

## Measures

**Cold Pressor Task (CPT)**—To assess adolescents' ability to manage a physiological stressor in an experimental, standardized manner (20) and evaluate changes in pain threshold, tolerance and intensity due to chronic nicotine use and withdrawal. The task was timed and all instructions were recorded in order to ensure consistency. At task initiation, participants were asked to immerse their right hand up to their wrist in water maintained at room temperature for 60 seconds to ensure that there were no inter-participant differences in hand temperature prior to cold water exposure. At the end of the one-minute period, subjects were asked to remove their hand from the water and immerse their hand into cold water maintained at 3–4°C for 90 seconds. Subjects were told to inform the researcher when they first felt pain and the time and rating were recorded. At the end of 90 seconds, if the subject's hand was still in the cold water, they were asked to remove it. Pain ratings were obtained using a visual numerical rating scale ranging from 0 (not at all painful) to 100 (extremely painful) with additional labels on 25 (somewhat painful), 50 (moderately painful) and 75 (very painful). Pain ratings were obtained every 15 seconds during the 90 second CPT and every 30 seconds for 2 minutes following task completion. If subjects removed their hand from the cold water before the 90 seconds were complete, then pain ratings were obtained at the time of hand removal (PI) in addition to the aforementioned times. The CPT has been shown to be safe and effective for measuring pain in a pediatric population and reduces the potential impact of confounding variables on outcome measures.

**Cardiovascular Measures**—Heart rate and blood pressure were assessed using a Dinamap oscillometric monitor (Critikon, Tampa, FL) at baseline (five minutes prior to CPT), the end of the 60 second exposure to the room temperature water, 45 and 90 seconds following initiation of CPT and every 60 seconds following CPT completion for 2 minutes. Cardiovascular responses were measured at these times even if the participants removed their hands before the end of the 90 second immersion period.

**Minnesota Nicotine Withdrawal Scale, Self-Report**—A 9-item scale used to assess nicotine craving and withdrawal. (21) This was administered prior to the CPT.

## Statistical Analyses

Adolescents were dichotomized into two groups, tobacco users and non-users. PTh was defined as the number of seconds until a participant first reported feeling pain in the cold water. PTo was defined as the number of seconds that a participant was able to keep his/her hand in the cold water. If his/her hand was immersed for the entire 90 second period, then that was considered to be the PTo level. Hand removal pain rating was defined as the rating of pain at the end of the 90 seconds or at the time that the hand was removed from the cold water.

Baseline characteristics by smoking status or by gender were analyzed using general linear models for continuous variables and Chi-square tests for categorical variables. Time to the first experience of pain had 3 levels – 15 seconds, 30 seconds and 90 seconds. Due to insufficient numbers at 90 seconds level, we dichotomized the measure into two groups (1: at 15 seconds, 2: at 30 seconds or higher). Chi-Square analysis was used to examine the differences in time to initial pain between smokers and non-smokers. Because all non-smokers experienced first pain at 30 seconds or higher, we further compared male smokers vs. female smokers using the Chi-square test and logistic regression. Because of the significant gender differences in years smoked, we treated it as a covariate. Pain intensity, pain tolerance, blood pressure and pulse were analyzed using mixed models. Smoking status (smoker, nonsmoker), sex (male, female), time (within subject factor, time 1: minimal/1-hour deprivation, time2: 42-hour deprivation) and their interactions were included in each analysis. The models with smallest BIC were selected to report the findings. Further, dependent measures of changes in blood pressure, craving and pulse were assessed using general linear models (GLM). Age was added to the models as a covariate. Associations of pain ratings with *Minnesota Nicotine Withdrawal* total score and craving measures were evaluated by Spearman correlations. Data analyses were conducted using SAS versions 9.3 and 9.4.

## Results

### Participant Characteristics

Ninety-six adolescents (mean age  $15.98 \pm 1.35$  years) were included. Age differed significantly between smokers and nonsmokers ( $p=0.0033$ ), however results were unchanged when controlling for age. Smokers had a mean Fagerstrom Test for Nicotine Dependence (FTND) score of  $3.96 \pm 2.20$ , Minnesota Nicotine Withdrawal Sale (MNWS) score of 5.23

$\pm 4.85$ , with  $13.28 \pm 7.04$  mean cigarettes smoked/day and mean years of smoking of  $2.40 \pm 1.70$ . There were significant differences in cigarettes smoked/day between sexes (females- $10.93 \pm 5.48$ ; males- $15.73 \pm 7.72$ ;  $p=0.012$ ).

### Pain Threshold

Pain threshold differed between smokers and nonsmokers. All non-smokers experienced their first pain at or after 30 seconds level, while only 20 (38.46%) smokers experienced the first pain  $\leq 30$  seconds ( $p<.0001$ ). There were no gender differences in smokers  $\leq 30$  seconds level: 11 (42.3%) male vs. 9 (34.6%) female,  $\chi^2=0.32$ ,  $p=0.569$ . Controlling for smoking related measures didn't change this finding.

### Pain Tolerance

We observed a significant main effect of smoking status [ $F(1, 91)=8.99$ ,  $p=0.004$ ] with significantly lower PTo levels in smokers than nonsmokers ( $55.7 \pm 28.8$  versus  $71.0 \pm 27.1$ ). In addition, we also observed significant effects on time [ $F(1, 92)=6.82$ ,  $p=0.01$ ], two-way (smoking status X sex;  $F(1, 91)=12.75$ ,  $p=0.001$ ) and three way (smoking status X sex X time;  $F(1,92)=4.88$ ,  $p=0.03$ ) interactions. Pain tolerance decreased from 64.9 seconds at minimal deprivation to 60.2 seconds at 42-hour deprivation. Comparison of least square means indicated that male smokers had greater pain tolerance than female smokers ( $p=0.0001$ ). Female nonsmokers had higher pain tolerance than female smokers ( $p<0.0001$ ). Pain tolerance decreased significantly over time for male smokers (75.5 seconds at the outpatient visit to 63.9 seconds at the inpatient visit;  $p=0.0004$ ), but didn't change much for male non-smokers (65.2 seconds outpatient to 65.4 seconds inpatient).

### Pain Intensity

Analysis of pain intensity revealed significant effects on time [ $F(1/92)=4.94$ ,  $p=0.03$ ], smoking status by gender interaction [ $F(1/91)=7.43$ ,  $p=0.01$ ] and smoking status by gender by time interaction [ $F(1/92)=4.77$ ,  $p=0.03$ ]. Pain ratings increased from 75.4 at minimal deprivation to 80.9 at 42-hour deprivation. Male smokers had lower pain ratings than female smokers ( $p=0.0185$ ). Pain didn't change over time for male non-smokers (84.5 at the outpatient visit to 84.7 at the inpatient visit), but increased significantly for male smokers (64.6 outpatient to 75.0 inpatient;  $p=0.0244$ ). Pain increased significantly over time for female non-smokers (68.2 outpatient to 78.8 inpatient;  $p=0.0269$ ), but didn't change for female smokers (85.7 outpatient to 85.7 inpatient).

### Cardiovascular Measures

Pre-task, there were significant two-way interactions for smoking X time [ $F(01/79)=4.55$ ,  $p=0.036$ ] for systolic blood pressure (SBP), and [ $F(01/80)=4.38$ ,  $p=0.0395$ ] for diastolic blood pressure (DBP). There was also a significant difference in DBP for smokers at minimal deprivation versus 42-hour deprivation ( $p<0.0001$ ). Further, there was a significant difference in DBP at minimal deprivation as compared to 42-hour deprivation among female ( $p<0.0001$ ) and male ( $p=0.0121$ ) smokers. There was a significant two-way interactions for smoking X time [ $F(01/79)=13.15$ ,  $p=0.005$ ] for pulses. At minimal deprivation, smokers had higher pulses as compared to nonsmokers ( $p=0.0074$ ).

During the CPT, smokers and nonsmokers experienced similar changes in SBP, DBP and pulse. During the post-task, CPT recovery (up to 120 seconds following hand removal) phase, nonsmokers exhibited greater changes in pulse than smokers ( $p=0.0004$ ), with a trend toward significance by sex ( $p=0.0549$ ).

### Withdrawal and Craving

For smokers, withdrawal was only associated with pain ratings 15sec after hand submersion at 42-hour deprivation ( $p=0.003$ ). Withdrawal was not significantly correlated with any objective CPT measures or with subjective pain at any other time points during or following minimal deprivation or acute abstinence. Craving was not associated with pain ratings at any time during the CPT at either session.

### Discussion

Smokers demonstrated lower pain threshold and tolerance as compared to non-smokers. We also found that adolescent female smokers have a significantly lower PTo than adolescent female nonsmokers and male smokers and nonsmokers following minimal and 42-hour deprivation. Further, male smokers displayed time-dependent decreases in PTo, wherein PTo decreased significantly following 42-hour deprivation when compared with minimal deprivation. One potential explanation for the significantly lower levels of PTo in female smokers after minimal deprivation as compared to male smokers, and significant decrement in PTo within male smokers from minimal deprivation to acute abstinence, could be differences in rates of loss of chronic tolerance to the analgesic effects of nicotine. Development of tolerance to the analgesic effects may also have contributed to the finding of smokers reporting pain significantly earlier following hand submersion (increased sensitivity), and female smokers displaying significantly briefer durations of hand submersion as compared to their non-smoking counterparts. This has considerable implications for smoking cessation interventions, as smokers, particularly females, may be less able to tolerate the discomfort associated with physical withdrawal symptoms that arise during cessation. This may in turn increase the likelihood of relapse to smoking as the literature suggests that smokers are more likely to relapse in response to painful stimuli. (22)

Reduced PTo may contribute to reinforcement of nicotine dependence as studies show that smoking may be used to relieve or avoid pain while exacerbating or initiating the occurrence of pain. (23) This phenomenon may lead to a positive feedback loop such that smoking may increase subjective experience of pain through reduced PTo and increased pain perception that is then eased by increased smoking leading to increased severity and frequency of pain and reinforcement and maintenance of nicotine dependence.

We also found Minnesota Nicotine Withdrawal Scores to be associated with pain fifteen seconds after pain induction during acute abstinence. This suggests that withdrawal is associated with acute experience of pain, as increased withdrawal scores predicted increased subjective pain at the first pain measurement time point. Withdrawal and craving do not appear to impact sub-acute pain as they were not associated with later time points during exposure to painful stimuli, nor subjective pain ratings 30–90 seconds after pain induction. This may be due in part to the impact of psychological factors on the experience of pain.

While extrapolating adult data to adolescents is inappropriate given differences in smoking trajectories and pain experiences, our findings mirror those in the adult literature in some respects. Cosgrove and colleagues have demonstrated that acute nicotine withdrawal, as well as short-term abstinence from smoking, may decrease pain threshold in adult smokers, (24) however this is the first replication of similar results of withdrawal impacting the acute experience of pain in adolescent smokers. The implication is that adolescents making quit attempts may resume smoking as a means to modulate pain.

Our findings of reduced PTo and PTh in adolescent smokers and smoking and sex differences in PTo and PI are novel in the adolescent smoking literature, as such we look to 11 adult studies for guidance in explaining sex differences. Potential mediators of the sex difference in these pain constructs that have been proposed include hormonal variations throughout the menstrual cycle in females. Estrogen has been found to enhance PTh; however we cannot attribute differences to this solely as female smokers demonstrated increased physical distress as compared to their female non-smoking counterparts. Additionally, it has been suggested that attention to pain may differ by gender, such that males report less fear of, and less attention paid to painful stimuli relative to age-matched females. (25) Enhanced coping skills and greater self-efficacy may play a role in diminishing the attentional narrowing caused by nicotine, as it introduces a distracter from the acute awareness of pain, allowing for shifts in attention to an alternate salient cue. It also improves an adolescent's belief in, and motivation for, successful cessation, as well as better mental preparedness for the challenges of quitting. For example, Ditre and colleagues demonstrated that those smokers who received coping enhancement and positive self-efficacy therapy prior to engagement in the CPT were better able to tolerate pain with improved pain perception, demonstrated longer latencies to resumption of smoking and reduced craving. (23)

Additional examination of the nicotine-pain relationship across multiple pain modalities, including electrical, thermal, mechanical, ischemic and chemical, are warranted as there is evidence that there may be baseline sex differences in some (i.e. electrocutaneous) but no other (i.e. thermal) subsets of pain. (2, 3) The effect of the sex and smoking status interaction with pain modality is inconclusive in adults and remains to be investigated in an adolescent population. Additionally, pain perception and tolerance in varying conditions such as time since last cigarette or stressed versus relaxed states is warranted as there is some evidence in the adult literature that stress may modulate the interaction between smoking and pain perception/tolerance in discreet modalities of pain. (2)

There are several limitations to this study. While the CPT has been shown to adequately induce subjective pain similar to that felt in clinical pain syndromes, it remains a laboratory-contrived phenomenon with high internal validity but somewhat limited external validity. There may have also been a learning effect related to pre-, post- administration of the CPT. Also, we did not control for time of last cigarette during the outpatient session. As a result, there were statistically significant differences between male and female adolescent smokers in breath CO levels, an indicator of recency of smoking. Therefore, while it is possible that the differences observed between male and female smokers at the outpatient session could be related to differences in minimal deprivation status, covariate analyses conducted using

the outpatient breath CO levels indicated no changes in the pattern of pain tolerance responses. All nonsmokers reported the same time of pain onset, which may have been due to false reporting. Additionally, we only evaluated pain within the context of acute abstinence, limiting our ability to extrapolate our findings to the entire cessation process. Nonetheless, since adolescents smoking for at least 6 months were assessed, we were able to derive useful data on the acute cessation experience of regular smokers. Finally, we did not assess, nor control for, group differences in pain sensitivity that may have existed prior to the onset of smoking. As such, there may have been other factors that contributed to pain differences between smokers and non-smokers. Since the days immediately following quitting are the most difficult in the cessation process, our evidence suggests that cessation interventions that provide increased support around subjective pain may be more successful.

## Conclusion

This study provides preliminary evidence of a relationship between chronic smoking and pain in adolescent females in regards to measureable decrements in PTo during minimal and 42-hour deprivation, and PI during minimal deprivation. As adolescent female smokers experience greater nicotine craving (26), more withdrawal symptoms, (27, 28) and greater difficulty achieving smoking cessation (16) at baseline, the possibility of an additional stressor of decreased ability to tolerate physical withdrawal symptoms may indicate that females may require more individualized intervention to address the varied contributors to the difficulties of achieving and maintaining abstinence. Further research is needed to clarify these relationships and the mechanism of the relationships between smoking, pain and sex.

## Acknowledgments

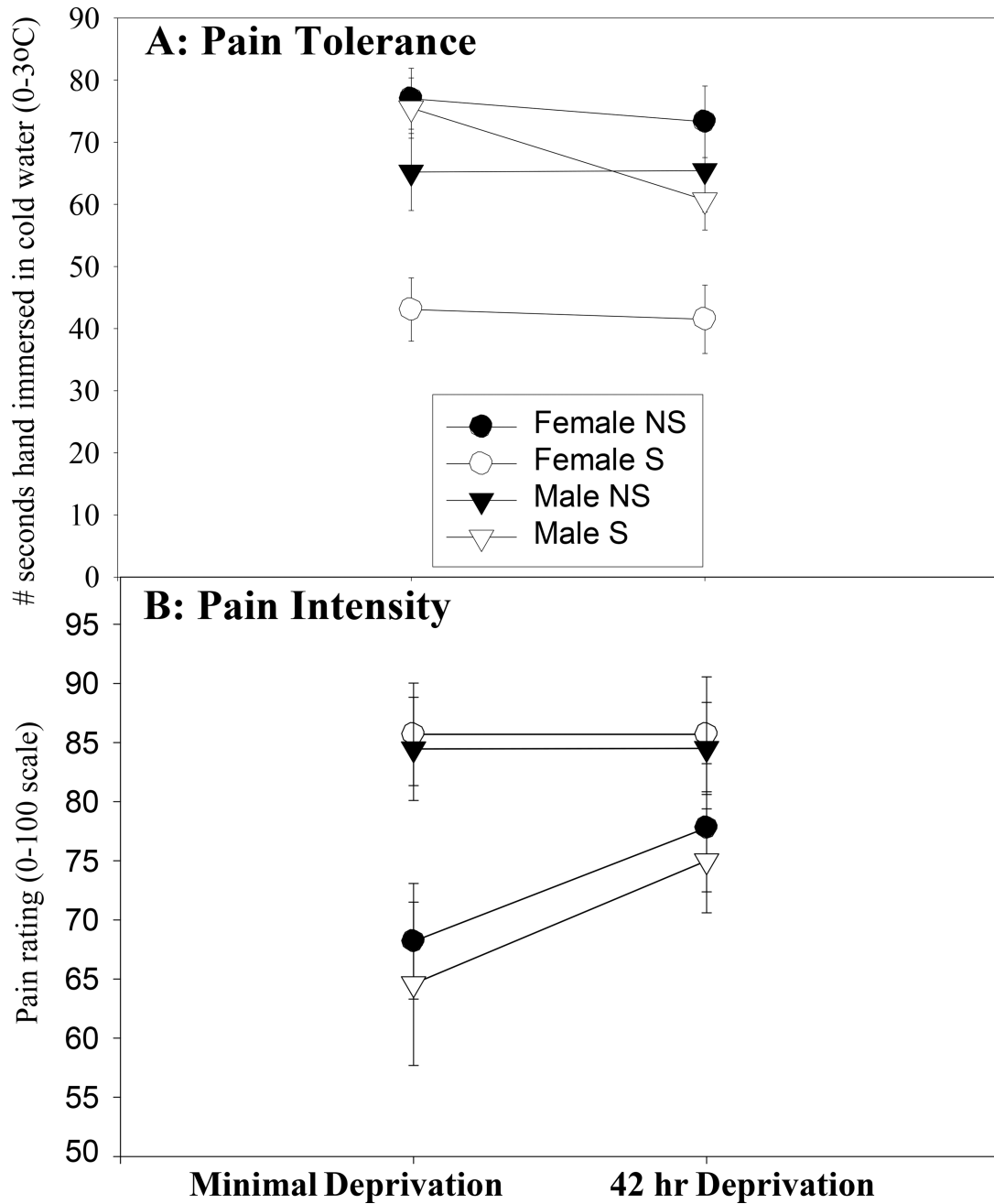
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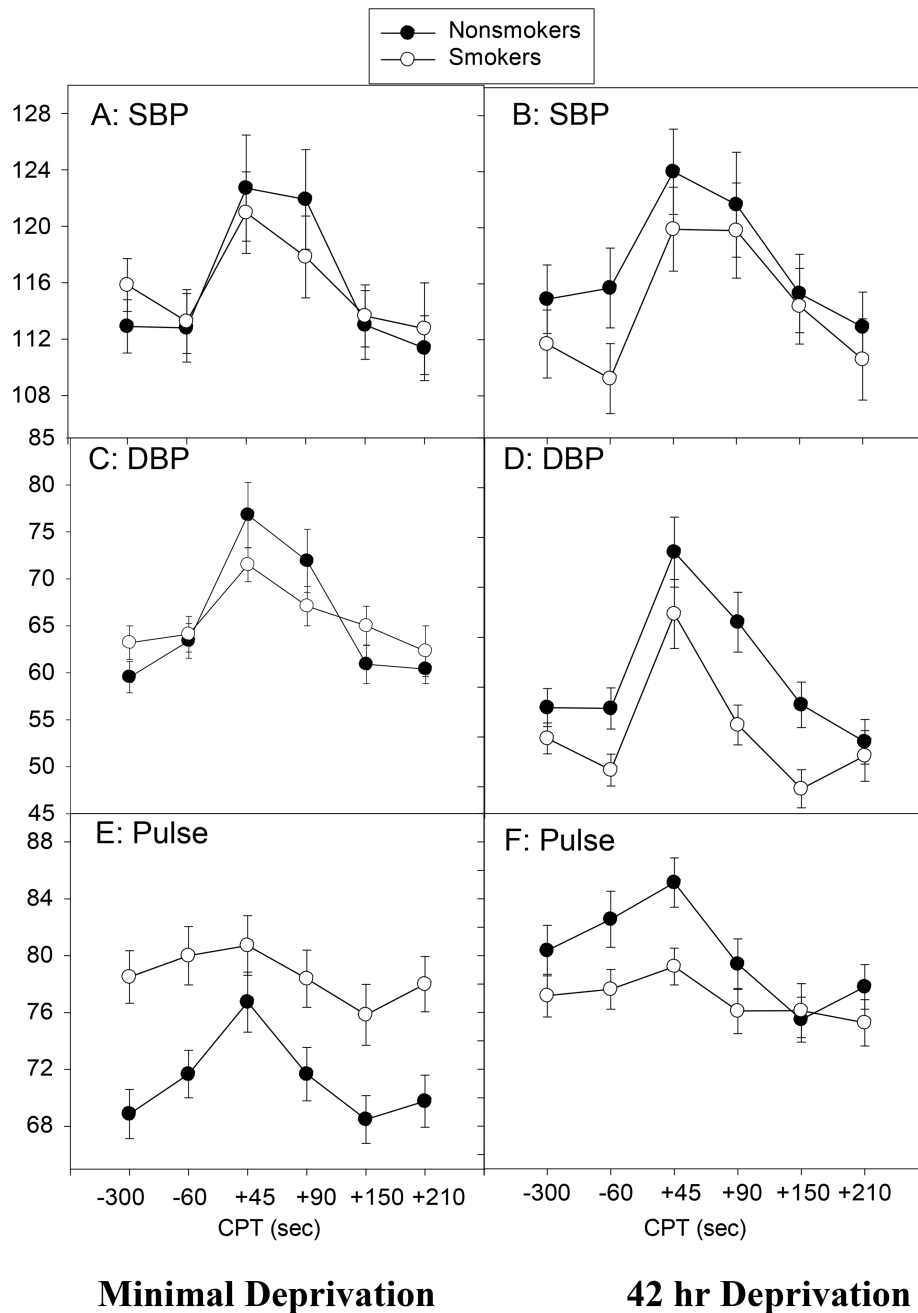
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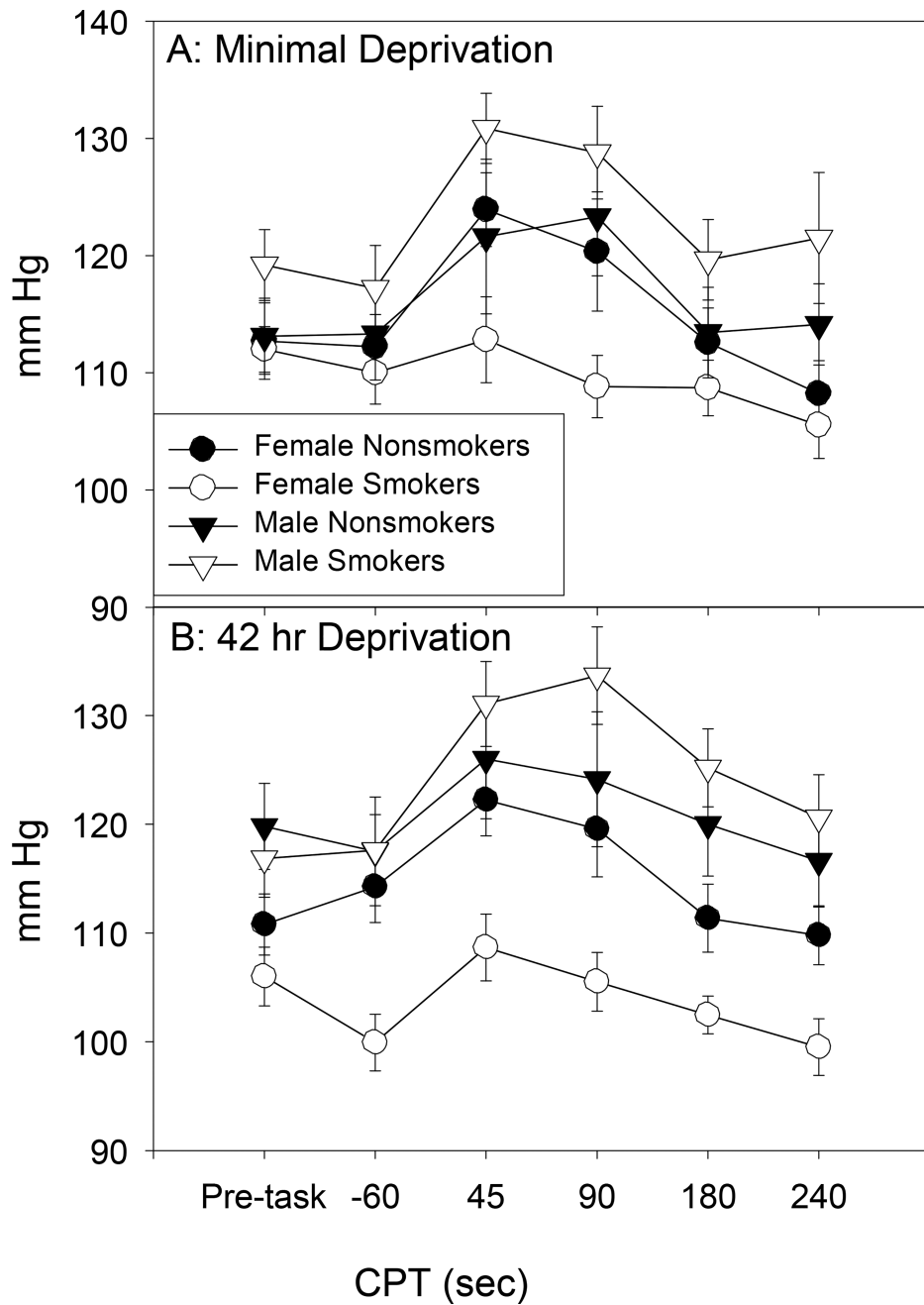
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**Figure 1.** Pain tolerance (A) and Pain rating (B) in smokers and nonsmokers during minimal deprivation and following 42 hours of deprivation from tobacco.  
 \*A: Pain Tolerance ( $p < 0.05$ ): Female smokers < Female nonsmokers, Male smokers, Male nonsmokers Male smokers-42 hr < Minimal deprivation  
 B: Pain Intensity ( $p < 0.05$ ): Minimal deprivation: Female smokers > Female nonsmokers, Male smokers Male smokers: 42 hr > Minimal deprivation



**Figure 2.** Systolic (A & B) and Diastolic (C& D) blood pressure and pulse rate (E & F) around CPT. Panels A, C and E were obtained during the CPT conducted while smokers were minimally deprived from tobacco and B, D and F were obtained during the CPT conducted following 42 hours of tobacco deprivation.  
 \*C: Nonsmokers>Smokers ( $p<0.01$ )  
 D: Smokers>Nonsmokers ( $p<0.01$ )  
 E: Smokers>Nonsmokers ( $p<0.01$ )



**Figure 3.** Systolic blood pressure in male and female smokers and nonsmokers during the Cold Pressor task (CPT) conducted when smokers were minimally deprived (A) or in 42 hours of deprivation (B).

\*B: Female smokers < Male smokers ( $p < 0.01$ ), Male nonsmokers ( $p < 0.01$ ), Female nonsmokers ( $p < 0.05$ )

**Table 1**

## Demographics-Baseline

Characteristics	Sample (N=96)	Smokers (N=53)	Non-smokers (N=43)
Age *	15.98 (SD=1.35)	16.34 (SD=1.25)	15.53 (SD=1.33)
Gender (# female)	51 (53%)	27 (51%)	24 (56%)
Race (# Caucasian)	67 (70%)	36 (68%)	31 (72%)

\* Significant difference between smokers and non-smokers ( $p=0.0241$ )

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**Table 2**

## Smoking Characteristics-Baseline

Characteristics	Female Smokers (N=27)	Male Smokers (N=26)	Significance
Age	16.26 (SD=1.26)	16.42 (SD=1.27)	$p=0.993$
Years Smoked	2.11 (SD=1.34)	2.69 (SD=2.00)	$p=0.217$
FTND	3.41 (SD=2.06)	4.54 (SD=2.23)	$p=0.061$
MNWS	5.74 (SD=4.90)	4.68 (SD=4.84)	$p=0.437$
Current cigs per day	10.93 (SD=5.48)	15.73 (SD=7.72)	$p=0.012^*$
Carbon monoxide (CO)	11.0 (SD=1.3)	14.25 (SD=1.7)	$p<0.05^*$
Craving	28.31 (SD=14.56)	26.06 (SD=15.07)	$p=0.321$

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