ABSTINENCE-INDUCED DECREMENTS IN ATTENTION PREDICT OUTCOME IN CIGARETTE SMOKING CESSATION

by

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Thesis submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences
In partial fulfillment of the requirements for the degree of
Master of Science 2014

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February 26, 2014

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ACKNOWLEDGEMENTS

First and foremost, I thank my Lord and Savior Jesus Christ, whose provisions sustain me through challenging times. Praise Him for He is good; His love endures forever (Psalm 106:1). I would also like to give sincere thanks to my family and friends from California for their enduring love, understanding, and support. I am blessed to have them in my life.

I am deeply appreciative for my advisor, Dr. Andrew Waters, and the committee members, Drs. Neil Grunberg and Mark Ettenhofer. Their wisdom, time, guidance, and support have been beyond measure. I would also like to thank the MD Anderson collaborators and research participants. This project would have been impossible without them. Additionally, I'd like to especially recognize my former lab members who were vital to the USU arm of Project Cognition. I am truly grateful for the valuable friendships I've been blessed with through LOCI and more broadly, through USU. I will always cherish the emotional support, companionship as well as tangible provisions afforded to me throughout my time so far at USU.

Finally, I would like to recognize all the support and assistance I have received from the MPS department faculty and administrative staff as well as the Graduate Education office; this project would not have been completed without them.

DEDICATION

To my undergraduate NIMH COR faculty mentors, Drs. John Jung and Chi-Ah Chun, who have been instrumental in my career path. I would not be where I am today without them.

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ABSTRACT

Abstinence-induced Decrements in Attention Predict Outcome in Cigarette Smoking Cessation:

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Cigarette smoking continues to be the leading cause of preventable death in the United States and is associated with economic costs to the individual as well as the society. The majority of smokers report being motivated to quit, however many quit attempts are unsuccessful, even with the use of the best available cessation interventions. Much research has examined psychological processes underlying relapse to smoking. Attention difficulty is a common withdrawal symptom, has been consistently found on subjective and objective measures of attention, and may contribute to smoking relapse. Clarification of the impact of withdrawal-related attention problems on smoking outcomes will help elucidate the underlying cognitive factors to smoking relapse.

The present study investigated the association between abstinence-induced attention difficulties and subsequent smoking status in nicotine-dependent smokers (*N*=193) attempting to quit smoking. Participants were followed from two weeks prior to quit day through four weeks post quit day. Before one pre-quit visit participants smoked

as usual, and before another pre-quit visit participants were instructed to remain abstinent for at least 12 hours. During the pre-quit visits, participants completed the Concentration Difficulty subscale of the Wisconsin Smoking Withdrawal Scale and the Rapid Visual Information Processing (RVIP) task. The primary outcome variable was point prevalence smoking status four weeks post quit day (end of study).

As expected, abstinence-induced declines in performance were obtained for Correct Hits (accuracy) and reaction times (RTs) for Hits on the RVIP task. Self-reported concentration problems did not correlate with objective indices of attention (RVIP) (*p*'s >.05). Follow-up analyses indicated a significant abstinence-induced difference in Hits and RTs for Relapsers at Week 4 (*p's* < .05), but not for Abstainers. Subsequent Relapsers exhibited abstinence-induced declines in performance, whereas Abstainers did not. Using hierarchical logistic regressions, abstinence-induced decrements in RVIP RT (odds ratio [*OR*] = 1.55; 95% confidence interval [*CI*] = 1.03-2.34; $p < .05$) and Concentration Difficulties (*OR* = 1.56; 95% *CI* = 1.05-2.31; $p < .05$) predicted subsequent relapse. As abstinence-induced RT and concentration difficulties got worse, there was a 55% and 56% increase in the probability of relapse 4 weeks later, respectively. In sum, abstinence-induced attention declines were associated with worse cessation outcomes.

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LIST OF ABBREVIATIONS

AUDIT = Alcohol Use Disorder Identification Test

CANTAB = Cambridge Neuropsychological Test Automated Battery

CD = Concentration Difficulty subscale of the WSWS

CDC = Centers for Disease Control and Prevention

CO = carbon monoxide

CPT = Continuous Performance Test

FA = false alarms

FTND = Fagerstrom Test for Nicotine Dependence

MINI = Mini International Neuropsychiatric Interview

PHQ = Patient Health Questionnaire

REALM = Rapid Estimate of Adult Literacy in Medicine

RIPT = Rapid Information Processing Task

RT = response time

RVIP = Rapid Visual Information Processing task

RVP = Rapid Visual Performance task

TOVA = Test of Variables of Attention

USUHS = Uniformed Services University of the Health Sciences

UT MDACC = University of Texas, M.D. Anderson Cancer Center

WM = working memory

WSWS = Wisconsin Smoking Withdrawal scale

CHAPTER 1: General Introduction

CIGARETTE SMOKING EPIDEMIOLOGY

Although there are a variety of tobacco products that contain nicotine, such as chewing tobacco, the current paper will center on cigarette smoking. This section on cigarette smoking epidemiology will highlight relevant populations that smoke cigarettes to emphasize the ubiquity of its use.

Prevalence

Cigarette smoking is pervasive globally (c.f., [119]) as well as nationally (e.g., [16, 107]). The present paper focuses on statistics for the United States. A 2011 CDC report (16) revealed that among adults, approximately 20% are current cigarette smokers. There is, however, a larger percentage of smokers (approximately 33%) who are active duty in the military (8, 9). Cigarette smoking is also common among youth under the legal age to purchase tobacco products in the United States. Surveys conducted by the Centers for Disease Control and Prevention (2012) (16) indicate that 4% of middle-school aged students reported smoking cigarettes in the past month, while 16% of high-school students reported smoking in 2011. Among under-aged youths, the 12-17 year-old age range has the highest smoking prevalence with 15% of adolescents reporting smoking within the past month in 2011 (107).

However, there has been an overall trend of declining cigarette use from 2002 to 2011 (107). Specifically, 26% of individuals aged 12 and older smoked in 2002, while the percentage decreased to 22% in 2011. Likewise for youths aged 12 to 17, the rates dropped from 13% in 2002 to 8% in 2011. Moreover, among current smokers, the percentage of individuals who smoked cigarettes daily decreased from 63% in 2002 to

61% in 2011. During the same time period, daily cigarette use among current smoking youths aged 12 to 17 decreased from 32% to 23% (107). In the US armed forces, rates of smoking dramatically decreased from 1980 to 1998 (51% to 30%), but increased to 34% in 2002 and have remained steady for four years thereafter (8).

Morbidity

There is considerable literature on the adverse health effects of cigarette smoking. Indeed smoking has consistently been widely known to be the leading preventable cause of morbidity and mortality (12, 13, 15). Smoking impacts the cardiovascular, pulmonary, and vascular systems, and can lead to lung and other cancers (13, 14). Additionally, smokers are at a two- to four-fold increased risk for stroke and coronary heart disease (13).

Military Readiness

Cigarette smoking also compromises military functions, including military readiness (70). In a study that followed new recruits for one year, smoking was found to be associated with premature discharge out of the military, which also led to excess training costs (56). Among the unfavorable findings were: poorer physical fitness evaluations, which is evident even among younger healthier personnel (17), an increased risk of sustaining injuries (57), and an overall increase in hospitalizations (87).

Mortality

As mentioned above, cigarette smoking is considered to be the leading preventable cause of death (12, 13, 15). Annually, there are more deaths from cigarette smoking than from HIV, substance use, suicides, and murders combined (14, 67).

Specifically, this quantity approximates to 400 thousand deaths per year that are attributable to the adverse effects of cigarette smoking (14).

Economic Cost

In addition to morbidity and mortality, there are associated financial ramifications of smoking. Cigarette use is the cause of more than $157 billion in annual health-related costs (14). The treatment for smoking-related diseases in the U.S., including lung cancer and heart disease, amounted to 6 to 8% of a smoker's yearly personal health expenditure (113). Furthermore, the reports from the CDC indicated that, overall, $96.8 billion are lost in productivity annually (14).

With respect to the armed forces, current smoking was associated with increased lost workdays due to hospitalizations for a range of health conditions (87). The Institute of Medicine reported that approximately $2 billion were spent by the DoD on smoking-related medical treatment, increased hospitalizations, and lost productivity annually (49). For the USAF alone, approximately $107 million per year was attributable to costs associated with current smoking; this estimate factored in lost work productivity as well as medical-related expenditures (11).

CIGARETTE SMOKING CESSATION BENEFITS

Health Benefits

Health benefits of smoking cessation are numerous. Advantages include improvements in the quality of life (72, 75, 82), as well as disease prevention or reduced risk for different types of cancer, coronary heart disease, stroke, and respiratory complications (22, 110). These health benefits subsequently reflect a risk reduction for premature death and an increased life expectancy (72, 75, 108, 110, 112). Furthermore,

findings suggest that this gain is not due to a trade-off between extended life and increased disability (72). Specifically, participants who quit smoking not only had lower mortality rates, but also had extended periods of decreased disability.

Economic Benefits

There are direct and indirect financial benefits to smoking cessation for the smoker as well as the society. Direct benefits include decreased healthcare expenditure for smoking-related disease treatment (75). Indirect economic benefits associated with smoking cessation are reflected as reduced work absenteeism and increased work productivity (63, 75).

CIGARETTE SMOKING QUIT ATTEMPTS

The majority (approximately 70%) of current adult smokers report being motivated to quit smoking and more than half of smokers attempted to quit in the previous year (16). While the best available treatments, including nicotine replacement and bupropion, improve cessation outcomes (52, 103), there are still many unsuccessful quit attempts. For instance, some studies report that of the smokers who attempted quitting, less than 10% actually succeeded. Indeed, smoking relapse is the most common outcome of cessation attempts (7, 15).

PSYCHOLOGICAL PROCESSES UNDERLYING SMOKING RELAPSE

Although, as noted above, relapse to smoking is the most common outcome of smoking cessation attempts, the psychological processes that cause relapse have remained unclear. Many researchers have focused on negative affect (e.g., [6]), and some relapses to smoking are preceded by acute increases in negative affect (99). However,

many relapses do not occur under high negative affect (98, 100). Recently, researchers have examined the role of cognitive processes in addiction and relapse (e.g., [104, 109, 117, 118]). For example, many researchers have examined automatic cognitive processes such as attentional bias (increased attention) to drug cues (26, 30). Other researchers have investigated the role of executive cognitive processes such as working memory (e.g., [76]).

The current study focused on the role of sustained attention and working memory in smoking relapse. A brief introduction to the concepts of sustained attention and working memory is provided below. In the following chapter, the literature on the effect of nicotine and nicotine abstinence on these processes is reviewed.

Sustained Attention and Working Memory

In the literature, there are several different models of attention. One well-known framework is Posner's model of attention (e.g., [77, 84, 85]). Posner proposes that attention is multidimensional with three discrete networks (alerting, orienting, and executive) that have different functions. Although the systems are largely independent, they work together. The "alerting" network functions to obtain and maintain a state of high sensitivity to incoming stimuli (i.e., to maintain alertness and awareness). Sustained attention is defined as the ability to maintain alertness for a prolonged period of time on a task (93). Sustained attention and vigilance are synonymous terms and will be used interchangeably throughout this manuscript. Vigilance is considered to be part of the alerting network. The "orienting" network serves to orient attention to sensory information while the "executive" network involves monitoring and regulating thoughts, feelings, and behaviors. The latter is considered to be a part of top down control (i.e.,

choosing to what to attend). The three discrete networks can be assessed using the Attention Network Test (ANT). However, early results in the nicotine literature have not shown that the task is sensitive to acute nicotinic manipulations (e.g., [69]).

Working memory refers to the temporary storage and manipulation of information in the mind. Similar to attention, there are numerous models of working memory. The current study extracts concepts from Baddeley's multicomponent model of working memory (e.g., [3, 4, 5]). Baddeley posits separable but interacting subsystems: a central executive and three sub-systems, including the phonological loop, the visuospatial sketchpad, and the episodic buffer. For the purposes of the current study, the central executive is the focus. The central executive, among other functions, is responsible for directing attention to relevant information, suppressing irrelevant information, and coordinating the slave systems.

A comparison of the previous two models reveals that Baddeley's central executive and Posner's executive control network are closely related. These systems generally perform the same functions, such as suppressing irrelevant information, attending to relevant information, and top down control. Therefore, working memory can be considered to be a part of the executive control network.

Application to Smoking Relapse

Researchers have operationalized attention lapses as slow response time on computerized tasks (e.g., [20, 66, 111]). As such, poor sustained attention (reflected by slow reaction time) can be indicative of attention lapses, which can lead to attention to salient stimuli (111) such as drug cues which are known to be hyper-salient for substance

mis-users (89). Along the same vein, working memory has been found to predict the ability to override extraneous stimuli (31).

To summarize, drug abstinence requires intact sustained attention and working memory and attention lapses can result in distraction toward salient drug cues or enable the drug seeking response to take over, thereby resulting in smoking relapse (see Figure 1 for concise summary of the conceptual model). For instance, intact top down processing and control may increase the ability to attend to relevant task-related information (such as abstinence maintenance) and to inhibit irrelevant information (such as prepotent salient drug cues), and thereby lead to maintenance of abstinence. Poor top down processing and control (such as attention lapses) may decrease the ability to attend to relevant task-related information (for example, abstinence maintenance) and to inhibit irrelevant information (i.e., prepotent salient drug cues), and thereby increase risk of relapse.

NICOTINE WITHDRAWAL

Attention difficulties are common during nicotine withdrawal. To meet DSM-IV-TR (2) criteria for a diagnosis of nicotine withdrawal, daily nicotine use for at least several weeks and abrupt reduction in use is followed by at least four signs within 24 hours: difficulty concentrating, dysphoric or depressed mood, insomnia, irritability, frustration, anger, anxiety, restlessness, decreased heart rate, increased appetite, or weight gain. Accordingly, many studies have assessed attention abilities using subjective and objective measures.

Withdrawal and Subjective Attention

In smokers attempting to quit, subjective reports of concentration difficulties are common and are consistent with DSM-IV-TR nicotine withdrawal (2). The severity of

nicotine withdrawal has been associated with clinically significant distress (43). Furthermore, some studies have found distinct differences in the withdrawal experience between lapsers and abstainers, such that lapsers reported more severe withdrawal symptoms relative to their counterparts (80). Moreover, the investigators found that symptoms were more intense on lapse days. Additionally, there is some evidence that withdrawal severity predicts relapse (1, 81, 114).

OBJECTIVE MEASURES OF ATTENTION

Laboratory studies investigating sustained attention and smoking have primarily used continuous performance task (CPT) paradigms to assess sustained attention performance, such as the Test of Variables of Attention (TOVA) and letter cancellation task (which are variations of CPT). Using the TOVA, one of the pioneering studies found that 24-hour nicotine deprived habitual smokers exhibited significantly greater variability in response latency compared to smokers smoking as usual and never-smokers (46). Response time and false alarms were also worse in abstinence, however these findings trended toward significance. Groups were matched on demographic factors and baseline TOVA performance for these analyses. Similarly, smokers were comparable on smoking behaviors including the number of years smoked, daily cigarettes smoked, and nicotine yield per cigarette. Furthermore, attention performance was not attributable to changes in mood. Using a different visual sustained attention task, letter cancellation, another classic experiment (74) found reductions on correct detections and response latency in habitual smokers deprived for at least 12 hours, whereas acute nicotine returned performance to baseline levels. Taken as a whole, findings suggest abstinence-

induced decrements in sustained attention and nicotine-induced improvements in sustained attention.

Effect of Acute Nicotine on Rapid Visual Information Processing Task Performance

One of the predominantly used CPTs in the nicotine literature is the Rapid Visual Information Processing Task (RVIP). There are a variety of names that refer to essentially the same task, including Rapid Information Processing Task (RIPT) and Rapid Visual Performance (RVP). This report employs the task name used in the respective journal articles. Overall, studies generally revealed consistent findings that the RVIP task is sensitive to the effects of nicotine. This summary is in light of employing varied methodological designs in moderate to heavy habitual smokers and never-smokers, varied nicotine doses, and an array of administration routes (e.g., [59, 62, 91, 115]). As such, for the purposes of the present study, the literature search was centered on studies utilizing the RVIP task (summarized in Table 1).

The literature can be summarized based on categorizing studies by the experimental manipulation of nicotine. The effect of nicotine on attention can be investigated by acutely administering nicotine (vs. placebo) (Table 1). The seminal 1983 study by Wesnes and Warburton (115), using a sample of habitual college-aged smokers, found that acute nicotine improved RIPT performance. In this study, improvements on response time and correct hits were exhibited in smokers who acutely received nicotine compared to their 24-hour deprived baseline levels (115) while similar enhancements were found by delivering nicotine via a transdermal patch (59). Moreover, these improvements were not attributable to a trade-off between the indices (115). A dose-response relationship was also revealed wherein the greatest improvements occurred with

the highest nicotine-delivering cigarettes (115); these effects were further refined with findings of curvilinear dose responses for both indices (73). Furthermore, performance on the RIPT diminished over time, parallel to reductions in nicotine levels.

These findings were replicated using a comparable methodological design, this time implementing a 12-hr deprivation period prior to smoking (21). In this study, the RVIP task was administered immediately after the experimental smoking session, when nicotine concentrations were the highest. However, not all studies found improvements with correct detections. Petrie and Deary (78) found improvements only on response latency.

Adding to this literature and further clarifying the nature of nicotine-induced attention enhancements, Kelemen and Fulton (55) found that improvements in sustained attention did not generalize to higher order cognitive processes, such as memory, in moderate smoking college students. Furthermore, a dose expectancy effect for false alarms and subjective concentration was found (53). That is, participants' commission errors (false alarms) and reported concentration problems worsened when expecting to smoke a placebo cigarette.

Although a majority of the literature has found improvements on the RVIP with acute nicotine, a number of studies revealed negative findings. Some studies reported that acute nicotine did not improve RVIP performance in habitual smokers (40, 71, 83) and never-smokers (27, 83). Herbert and colleagues (40) posited that the lack of a training period conducted prior to the actual trials might have introduced noise to the data, contributing to unclear interpretations. Nesic et al. (71) utilized a sample with a range of light to heavy smokers and a 5-minute abbreviated RVIP task. The authors

posited that the null findings might be attributable to practice effects. Despite the absence of effects in this study, the more severe nicotine dependent participants exhibited less improvement on RVIP indices relative to the low dependent subjects. This result suggests an effect of nicotine, albeit a differential impact on the groups. In a 2005 study by Poltavski and Petros (83), the absence of nicotine-induced effects was found using a 6-hour deprivation period and with the acute delivery of nicotine via a transdermal patch. The authors proposed a possibility that the 5-minute practice period (and 5-minute actual trials) may not have been sufficient time to establish optimal performance.

Of particular interest, Poltavski and Petros (83), Herbert et al. (40), and Nesic et al. (71) were not methodical in the design of the deprivation periods. For instance, the deprivation period prior to acute nicotine administration was unclear, the spectrum ranged from 1 and possibly up to 11 hours, the specified deprivation range encompassed a wide spectrum (e.g., 2 to 96 hours), and the deprivation period was relatively shorter than the studies that found nicotine-induced effects. The vast majority of studies that found positive effects utilized at least eight hours of deprivation (c.f., [21, 29, 55, 62, 73, 78, 115]), with a single exception of Juliano and colleagues (53) that employed a three-hour abstinence period.

To elucidate whether improvements in attention are attributable to absolute nicotine effects or simply the relief of nicotine withdrawal, never-smokers were recruited for the first time in the literature. Administering acute nicotine subcutaneous injections, Foulds and colleagues (29) found differential improvements on the RVIP task. With the administration of acute nicotine, nicotine-deprived smokers demonstrated increased correct hits and reduced response latencies, while never-smokers exhibited reduced

response latencies. Comparably, a study of never smokers employing a nasal spray for nicotine delivery revealed that nicotine improved RVIP response time compared to the placebo condition (91). No effects on correct hits or false alarms were found.

These positive findings in never-smokers provide support for absolute nicotine effects that are not due to withdrawal relief. Nevertheless, one study of never-smokers found that acute nicotine did not impact RVIP performance (27). The authors proposed that the absence of effects suggested not absolute nicotine effects but withdrawal relief. However, all subjects were never-smoking medical students and no comparison or control groups were included. This sample was particularly homogenous. Furthermore, these results need to be considered in light of the acknowledgement that never-smokers may be inherently different than regular smokers.

To summarize, the literature on acute nicotine administration has generally found improvements in performance on the RVIP task that, at least in never-smokers, is not due to withdrawal relief. These positive findings are consistent across varied methodological designs, nicotine administration routes, and deprivation periods prior to nicotine delivery, as well as sample demographic and smoking characteristics.

Effect of Acute Nicotine in Animal Models

Animal models further corroborate the findings from human studies on nicotine's involvement in sustained attention processes assessed on a serial reaction time task. Parallel to human studies, animal studies using mice and rats revealed that acute nicotine administration enhanced attention while acute nicotine deprivation reduced performance.

Acute nicotine administration in mice was associated with improved attention performance (e.g., [35, 102, 120]) while attention improvements were also found using a

two-choice stimulus detection task in middle- and old-aged rats (34). Improvements in attention performance were found in a dose-response pattern (e.g., [34, 106]) and were not attributable to changes in motor capacity, learning and memory, or changes in sensory capability (106). Improvements were also not due to withdrawal relief but were attributable to absolute effects from nicotine (36).

One study found that although initial disruptive effects of nicotine masked attention benefits, chronic effects of nicotine were associated with attention enhancement (36). However, another study found attention improvements in mice that were not previously administered nicotine (120).

Reversals of the attention performance improvements were observed with nicotine antagonists (e.g., [35, 102, 106]). Decrements in performance on sustained attention tasks were reflected as longer reaction times and decreased accuracy rates (e.g., [35, 106]) and increased omission errors (102). In addition to studies using nicotine antagonists, abstinence was produced by withdrawing nicotine from rats that were receiving chronic doses (95). Findings from this study revealed impaired performance on a sustained attention task.

In sum, a wealth of data from human and animal models reveal that sustained attention is sensitive to nicotinic manipulations, and that the RVIP task is a useful tool to examine these processes.

Effect of Acute Abstinence on Rapid Visual Information Processing Performance

The effect of nicotine abstinence on RVIP performance has been investigated by manipulating nicotine abstinence as an independent variable (comparing non-abstinent vs. abstinent smokers). Overall, studies of nicotine deprivation provide further support of

nicotine's impact on attention. Leventhal and colleagues (62) recruited moderate to heavy habitual smokers not attempting to quit. In this within-subject study design, participants were instructed either to smoke as usual or abstain from nicotine for at least 12 hours prior to completing the RIPT. Abstinence-induced decrements were found on RIPT performance, reflected by increased response latency and decreased correct detections. Additional analyses on the same dataset suggested there were no gender differences (61). A second study found similar results. Hendricks and colleagues (2006) (39) randomly assigned smokers to either smoke as usual or abstain from smoking. Abstainers exhibited slower reaction times relative to their closely matched smoking counterparts. Further, these decrements were found within 30 minutes of not smoking. Comparably, Kelemen & Fulton (55) found decreased hit rates and increased response times using moderate smoking college students not trying to quit. Participants abstained from nicotine for at least 8 hours in this study. In summary, results from studies inducing acute nicotine deprivation reveal that acute abstinence impairs performance on the RVIP.

Taken as a whole, these studies provide strong support that the RVIP task is sensitive to the effects of nicotine and nicotine abstinence. From a broader perspective, withdrawal symptoms can be a barrier to successful cessation efforts and this information may provide some insight on factors underlying successful versus unsuccessful quit attempts.

CORRELATION BETWEEN SUBJECTIVE AND OBJECTIVE MEASURES OF ATTENTION

A number of studies have failed to find an association between subjective and objective measures purported to assess similar constructs. In one study, smokers were randomly assigned to either smoke cigarettes as usual or abstain from smoking for 4

hours (39). Although withdrawal-induced decrements were found using the RVIP task and self-reported concentration problems endorsed using the WSWS, there was an absence of significant correlations between these assessments. Likewise, a review paper on withdrawal effects in smoking cessation, corroborates these findings (100).

CHAPTER 2: Introduction to the Current Study

RATIONALE FOR CURRENT STUDY

The rationale for the current study is as follows. The psychological processes that underlie relapse to smoking have remained unclear. Cognitive processes such as working memory and sustained attention may play a role. Specifically, there is evidence that performance on sustained attention tasks deteriorates during abstinence and these attention difficulties may promote relapse. However, few studies have examined the impact of attention deterioration on smoking. At the time of writing this manuscript, no studies have examined the clinical relevance of abstinence-induced attention problems assessed using the RVIP task. Therefore, the purpose of this study was to examine the association between abstinence-induced deficits in sustained attention and subsequent relapse to smoking.

Specific Study Aims and Hypotheses

In the current study, participants attempting to quit smoking were assessed on two occasions before the quit day: once when abstinent and another time when non-abstinent. Subjects were monitored for 4 weeks after the quit day. The specific aims and corresponding hypotheses based on the literature are as follows:

Specific Aim 1.1: To examine the effect of acute nicotine abstinence on RVIP performance in smokers motivated to quit smoking.

Hypothesis 1.1: Compared to performance in the non-abstinent session, participants in the abstinent session will exhibit decrements in RVIP performance, reflected by increased reaction time and decreased hits. The investigation of the effect of nicotine deprivation on false alarms will be exploratory; as such no direction is predicted.

Specific Aim 1.2: To investigate the effect of acute nicotine abstinence on the concentration difficulty subscale of the Wisconsin Smoking Withdrawal Scale.

Hypothesis 1.2: Participants in the abstinent session will report more concentration difficulties relative to the non-abstinent session.

Specific Aim 1.3: To evaluate the association between subjective and objective measures of attention.

Hypothesis 1.3: Subjective and objective indices of attention will not be significantly correlated.

Specific Aim 2: To investigate the clinical relevance of the subjective and objective measures of attention in smokers motivated to quit smoking.

Hypothesis 2: Both subjective and objective indices of attention difficulties will predict point prevalence abstinence at a one-month follow-up.

CHAPTER 3: Methods

The current study was part of a larger multi-site prospective cohort smoking cessation study. Sites were located at the University of Texas, M.D. Anderson Cancer Center in Houston, Texas, and the Uniformed Services University of the Health Sciences in Bethesda, Maryland. The Institutional Review Boards at the respective sites approved the study procedures (see Appendix B). Abstinence was experimentally manipulated in a within-subject design. Consenting subjects attended abstinent (at least 12-hour nicotine deprivation) and non-abstinent visits (*ad libitum* smoking prior to the laboratory visit) and the order of the abstinence sessions was counterbalanced. Refer to Appendix D for the USUHS informed consent form. Pharmacotherapy was not offered, but every subject received brief, individualized face-to-face and telephone counseling sessions.

RECRUITMENT PROCEDURES

A community sample was sought in accordance with the ethnic demographic breakdown of the respective geographical regions. Participants were recruited via media outlets, such as NPR radio and craigslist.com. In addition to local hospitals and clinics, recruitment advertisements were posted on organization websites such as SmokeFree.gov and MDQuit.org (in sections including classified advertisement or "research studies").

INCLUSION AND EXCLUSION CRITERIA

Potential participants were initially screened via telephone and if they met criteria, they were invited to the in-person orientation session where they underwent second-tier screening not feasible over the telephone. Potential participants were included in the study if they were between the ages of 18 and 65, a current smoker with a history of at

least ten cigarettes per day for the past year, and were motivated to quit smoking within the next four weeks. Participants were also included if they had a home address and a functioning telephone number, if English was their first language and they could speak, read, and write English at an 8th grade literacy level. Participants were excluded from the study for regular use of tobacco products other than cigarettes, such as cigars, pipes, and smokeless tobacco, nicotine replacement products, and/or use of varenicline or bupropion. They were also excluded for having an expired breath carbon monoxide (CO) level less than 10 parts per million to ensure regular cigarette use (c.f., [105]). Other exclusionary criteria included being pregnant or breast feeding, serious mental illness (specifically, endorsements of active suicide ideation or depression), current substance abuse or dependence, or if another household member was enrolled in the study.

STUDY PROCEDURES

Participants attended up to six laboratory visits, including the orientation session, two weeks prior to quit day through four weeks post quit day. At the orientation visit, participants completed the following measures: The Rapid Estimate of Adult Literacy in Medicine (REALM; [19]), Patient Health Questionnaire (PHQ; [58]), Mini International Neuropsychiatric Interview (MINI; [96]), Alcohol Use Disorder Identification Test (AUDIT; [94]), Shipley Institute in Living Scale (Shipley; [101]), Fagerstrom Test for Nicotine Dependence (FTND; [38]), and self-reported smoking status (which was biochemically verified using expired breath CO monitor). These measures will be described in detail in the measures section below. See Appendix E and F for questionnaire samples.

As mentioned before, the two pre-quit visits were counterbalanced: participants either smoked *ad-libitum* or abstained for 12 hours prior to these sessions. During these two pre-quit visits, participants completed the primary attention measures (Rapid Visual Information Processing task and Wisconsin Smoking Withdrawal Scale), the order of which was also counterbalanced, and these measures are described in detail later. Participants subsequently attended the quit day laboratory session, and returned for follow-up sessions one and four weeks later. Biochemically-verified point prevalence abstinence was determined at these three visits.

Counseling

All participants received up to five individualized face-to-face and up to two phone smoking cessation counseling sessions with trained, licensed masters-level therapists. This procedure was to comply with standard ethical guidelines in smoking cessation treatment (28). Sessions lasted up to 20 minutes and were based on tobacco use and dependence clinical practice guidelines that addressed coping and problem solving skills. Topics such as identifying high-risk situations, coping with negative affect as well as lapses, and relaxation techniques were offered. Each participant's unique barriers and high-risk situations guided the coping and problem-solving framework.

MEASURES

Baseline

Assessments administered during the orientation session included the following: REALM as a literacy screener, PHQ to assess for depressive symptomatology and suicidal ideation, AUDIT to screen for alcohol use disorders, MINI to evaluate any non-

alcohol psychoactive substance use disorders, as well as the Shipley to assess intellectual ability.

Fagerstrom Test for Nicotine Dependence

The FTND is a 6-item self-report measure employing a 10-point rating scale used to assess nicotine dependence and to quantify dependence severity (38). The FTND was used as a covariate in the main analyses as well to evaluate any baseline nicotine dependence differences between subsequent relapsers and abstainers.

Smoking Diary

Participants recorded their daily cigarette use with a smoking diary throughout the course of the study. Self-reports of smoking were biochemically-verified and the data contributed to the determination of smoking status.

Biochemical Markers

Biochemical markers were used to validate self-reported smoking behaviors. Cotinine is a major metabolite of nicotine. Saliva samples were collected and then sent to an external assay company (Salimetrics, LLC, State College, PA). Cotinine levels less than or equal to 15 nanograms per milliliter were considered to reflect abstinence. Saliva cotinine is considered the gold standard for determining nicotine exposure (50, 105), and is detectable up to seven days. However, the optimal detection is within two to three days and subsequently becomes less reliable with the passage of time.

Commercially available breath CO monitors (Bedfont Scientific Ltd., UK, Vitalograph, Lexena, KS) were used to determine recent smoking (up to 48 hours). Uptake of CO is related to the quantity of nicotine absorbed and this method is an indirect

measure of CO in blood. On the experimental session that required overnight nicotine abstinence, participants were required to have a CO level of less than or equal to 10 ppm. Carbon monoxide less than or equal to 10 parts per million is a standard cut-off which indicates abstinence (105).

Primary Measures

Subjective Attention

The Wisconsin Smoking Withdrawal Scale (WSWS; [114]) is a 28-item self-report questionnaire using a 5-point rating scale that assesses nicotine withdrawal symptoms. Higher scores indicate worse withdrawal symptoms. Subscales include Concentration Difficulty and Anger. For the purposes of this study, the Concentration Difficulty subscale was adapted to assess symptoms "right now" to match with the administration of the RVIP task. Items were "My level of concentration is excellent" which was reverse scored, "It is hard to pay attention to things," and "It has been difficult to think clearly." The instrument has shown strong psychometric properties. It has been reported to have good reliability and validity, has shown high sensitivity to withdrawal, and has been used to predict cessation outcomes (114, 116). Consistent with past research, strong internal consistency among the difficulty concentrating items was found in the current study. Specifically, Cronbach's alphas for the three items yielded good to excellent internal reliability at the Abstinent and Non-abstinent sessions, respectively (Table 2).

To cross-validate the Concentration Difficulty subscale, a single summary item "Right now, I am having difficulty concentrating" was used. This item was rated on an 11-point scale (0-10; higher scores indicating more difficulties) and is comparable to

items from other widely used withdrawal measures, such as the Minnesota Nicotine Withdrawal Scale (44). Pearson's correlations indicated that the single marker item and the Concentration Difficulty items were highly correlated reflecting strong concurrent validity for our sample (see Table 3).

Objective Attention

The RVIP task (Cambridge Cognition Ltd., Cambridge, UK) was used to assess visual sustained attention, which also has a working memory component. Psychometric properties have shown to be sound, including strong test-retest reliability (37). Indices, such as reaction time have also shown to be a good indicator of sustained attention and to be sensitive in detecting changes following pharmacological manipulation of nicotine (92).

The task was administered utilizing standardized CANTAB® hardware. The stimuli were presented on a portable tablet PC and responses were recorded on a two-button external press pad that was designed to provide millisecond accuracy. On the tablet PC, a white box appears in the center of the black screen. Inside the white box, digits from 2 to 9 appear serially in pseudo-random order at the rate of 100 digits per minute. A sample serial presentation is displayed in Figure 2.

A standardized set of instructions was provided at the outset of the training session. Participants were instructed to press the external press pad "as quickly as possible while avoiding mistakes" when they detected a 3-digit target (2-4-6, 3-5-7, or 4-6-8). The full task instructions can be found in Appendix A. Target sequences appeared at the rate of 16 every 2 minutes. Participants completed a 2-minute practice trial before continuing to the 4-minute test session. Total task duration was 6 minutes. Working

memory is required because the participants are to keep in mind the 3-digit targets while attending to serially presented stimuli. Maintaining attention during such a repetitive task for a prolonged duration requires sustained attention.

The outcome variables included: the number of correct hits (measured in counts), mean reaction time of correct hits (expressed in milliseconds), and the number of false alarms (indicated by counts). Correct target detections ranged from 0 to 27. Correct responses within a response window of 1800 ms were included. Higher number of hits indicated better performance. Mean RT was the time to correctly respond to a target within a response window of 1800 ms; slower reaction times indicated poorer performance. False alarms were the number of commission errors (calculated as a response outside of response window or multiple responses within the response window), and ranged from 0 to a maximum possible count of 273. Higher numbers of false alarms indicated poorer performance.

Smoking Status

Smoking status was operationally defined as point-prevalence at four weeks post quit day. To be coded an "Abstainer" at Week 4, a participant had to: 1) deny self-reported smoking for the past week, 2) have a breath CO level less than or equal to 10 ppm, and 3) have a saliva cotinine less than or equal to 15 ng/ml. All other participants were coded as "Relapsers," including participants who did not attend the Week 4 session.

ANALYTIC PLAN

Sample Characteristics

Demographic Information

Descriptive statistics (means, standard deviations, percentages) for variables obtained at baseline for the final sample were examined.

Smoking Characteristics

Similarly for smoking patterns, descriptive statistics (means, standard deviations, percentages) for the final sample were examined.

Missing Data

Overall, 268 participants attended the orientation session and signed the informed consent form. Of those 268 participants, 200 participants attended the two pre-quit sessions as well as the quit day session, and 68 participants dropped out prior to the quit day session. Compared to the individuals who attended the quit day session, the 68 "dropouts" were younger, t (266) = 2.59, $p < .05$, had smoked for fewer years t (265) = 2.82, $p < .01$, had lower Shipley IQ scores, t (264) = 2.80, $p < .01$, and reported a lower income, t (263) = 2.38, $p < .05$. They did not differ in gender, race, FTND, time to first cigarette in the morning, baseline CO level, saliva cotinine levels, number of past quit attempts, years of education, or study site (p's > .05).

Relapse data were available from the 200 subjects who attended quit day. However, due to equipment or researcher error, 7 subjects did not have RVIP data from both pre-quit sessions and they were excluded from the final analyses. Errors included non-functional external button press and the researcher's failure to administer the RVIP

task. Therefore, a sample size of 193 with complete RVIP data for both pre-quit visits was utilized for the primary analyses.

Given that the RVIP task was the primary measure of interest, the decision was made to ensure that statistical analyses were conducted on subjects with complete RVIP data. Accordingly, of the 193 subjects, there were complete WSWS data for 189 subjects. Four subjects were missing WSWS data due to experimenter or equipment error.

Primary Analyses

Specific Aim 1.1

To evaluate the effect of acute nicotine abstinence on objective measures of attention, a paired samples t-test was conducted for each RVIP index. The independent variable was Visit Type (2 levels: Abstinent vs. Non-abstinent) and the dependent variables were the RVIP indices (RVIP RT, RVIP Hits, False Alarms).

Specific Aim 1.2

To evaluate the effect of acute nicotine abstinence on subjective measures of attention, a paired samples t-test was conducted. The independent variable was Visit Type (2 levels: Abstinent vs. Non-abstinent) and the dependent variable was Concentration Difficulty on the WSWS.

Specific Aim 1.3

Pearson's correlation coefficients were conducted to evaluate associations between objective and subjective measures of attention. Correlations were conducted using absolute values of the attention measures obtained from the respective Visit Type

sessions (Abstinent and Non-abstinent) as well as difference scores calculated from these visits. Difference scores for each index were calculated by subtracting the Non-abstinent value from the Abstinent session values (i.e., score on Abstinent session – score on Non-Abstinent session). Larger difference scores for RT, False Alarms, and Concentration Difficulty reflected abstinence-induced problems, while smaller values for Hits indicated abstinent-induced difficulties. In all cases, 95% confidence intervals are provided to indicate the likely location of the population correlation, rho.

Specific Aim 2

Two strategies were employed to examine the association between attention measures and subsequent smoking status. The general linear model was employed as the first strategy. A series of univariate mixed repeated-measures ANCOVAs were conducted with RVIP indices (RT, Hits, False Alarms) and Concentration Difficulty as the dependent variables. The within-subject independent variable was Visit Type (Abstinent vs. Non-abstinent) and the between-subjects independent variable was Smoking Status at Week 4 (Abstainer vs. Relapser). Covariates included were FTND and the Order (Non-Abstinent first vs. Abstinent first). Of interest was the Smoking Status x Visit Type interaction.

A series of univariate hierarchical logistic regressions was conducted as the second strategy. This method was conducted in two stages. Stage one evaluated RVIP RT and Hits entered together as a block. In block one, the covariates Order and FTND were entered and in block two, RVIP RT and Hits were simultaneously entered. This analysis allowed the determination of whether the RT and Hits measures entered together as a block significantly predict relapse, and provided protection against type I error. In

stage two, Order and FTND were entered into block one and individual predictor variables were entered separately. In all models, the predictor variables were difference scores for RVIP RT, Hits, and Concentration Difficulty and the outcome variable was Smoking Status at Week 4.

Power Analyses

Power analyses were computed using G*Power 3.1.2. Power estimates for 2-tailed tests were set at alpha level of .05. For a sample size of 189, 80% power would enable detection of a population correlation coefficient (ρ, rho) of 0.202 (indicating a small to medium effect) between the independent and dependent variables, controlling up to two covariates.

CHAPTER 4: Results

SAMPLE CHARACTERISTICS

Demographic Information

The final sample of 193 subjects was biochemically verified habitual smokers motivated to quit smoking. Demographic data by site and combined are presented in Tables 4-6. Forty-two percent of the sample was recruited at USUHS in Maryland and the remainder was enrolled at The University of Texas M. D. Anderson Cancer Center in Texas. Fifty-five percent of the sample was Male, 55% self-identified as White, 37% self-identified as Black, and 8% as Other. The mean age was 44 years. Reported average annual family income before taxes for the sample was between $40,000 and $50,000. Reported number of year of education was 14.25 years and the mean IQ level for the sample was 104.41, as assessed by the Shipley.

Smoking Characteristics

Overall, this was a moderate to heavy smoking sample (Table 4). The mean nicotine dependence score, assessed using the FTND, was 5.2 reflecting moderate dependence, and 86% of the sample reported smoking their first cigarette of the day within 30 minutes of waking. Baseline levels of expired air carbon monoxide for the sample averaged at 21.05 ppm. Saliva cotinine levels at the non-abstinent session were 383.16 ng/ml, indicating a heavy smoking sample (saliva cotinine levels greater than 100 ng/ml is considered to indicate regular smoking [23]). The reported average number of cigarettes smoked daily was 19.5 (about a pack of cigarettes). The reported mean years smoked was 24.15. The mean number of reported lifetime quit attempts, defined as staying quit for at least 24 hours, was 5.3.

PRIMARY ANALYSES

Specific Aim 1.1

The summary statistics on the RVIP are presented in Table 7. The effect of acute nicotine abstinence on objective measures of attention was analyzed using paired samples t-tests, as described above. Significant t-values were obtained for RVIP Hits (t [192] = 2.00, $p < .05$, $d = 0.14$), and RT (t [192] = -2.46, $p < .05$, $d = 0.18$). On both these measures, participants exhibited significantly worse performance at the Abstinent visit compared to the Non-abstinent visit. There were no significant differences in RVIP False Alarms between the Abstinent and Non-abstinent sessions (t [192] = -0.27, $p > .05$, $d = 0.02$).

Specific Aim 1.2

The summary statistics on the WSWS difficulty concentrating by Visit Type are presented in Table 7. The effect of acute nicotine abstinence on WSWS difficulty concentrating ratings was analyzed by a paired samples t-test. A significant t-value was obtained for WSWS Concentration Difficulty (t [188] = 6.43, $p < .001$, $d = 0.47$) and the Summary Score (t [188] = 6.48, $p < .001$, $d = 0.47$). Subjects reported significantly greater concentration problems during the abstinent session relative to the non-abstinent session.

Specific Aim 1.3

Associations between objective and subjective measures of attention were analyzed using Pearson's correlation coefficient. Pearson's correlation coefficients using absolute values revealed non-significant r values between RVIP indices and the Concentration Difficulty items at the Abstinent session (see Table 8) as well as at the

Non-abstinent session (see Table 9). Likewise, Pearson's correlation coefficients using difference scores revealed non-significant associations between RVIP indices and WSWS Concentration Difficulty as well as the Summary item (see in Table 10).

In general, visual inspection of the data (Tables 8-10) reveals that the absolute magnitude of the correlations was small. For example, none of the correlations involving difference scores (Table 10) had an absolute magnitude greater than ±.07. Moreover, the confidence intervals reveal that the true correlation in the population, rho, is unlikely to be more extreme (further from 0) than ±.21 (a small to moderate effect size). Therefore, although the current data do not, by any means, "prove" the null hypothesis that the variables are uncorrelated (rho = 0) they do suggest that the true correlation in the population is unlikely to be any larger than a small-to-moderate effect.

Specific Aim 2

The summary statistics for Relapsers and Abstainers are presented in Table 11. A series of univariate mixed repeated-measures ANCOVAs was used as the first strategy to examine the association between attention measures (RVIP RT, RVIP Hits, RVIP False Alarms, Concentration Difficulty) and subsequent smoking status, controlling for FTND and Order of abstinent session.

For RVIP RT, results indicated a significant Smoking Status by Visit Type interaction (F [1, 189] = 4.56, $p < .05$, $\eta_p^2 = .024$) (see Figure 3). Follow-up simple effects analyses revealed that for Abstainers, there was no significant difference in RT between the Abstinent and Non-abstinent sessions ($p > .05$). However for Relapsers there was a significant difference in RT between the Abstinent and Non-abstinent

sessions ($p < .01$). Subsequent Relapsers exhibited abstinence-induced decrements in RT, whereas the Abstainers did not.

For RVIP Hits, there was a non-significant Smoking Status by Visit Type interaction (F [1, 189] = 2.57, $p > .05$, $\eta_p^2 = .013$; Figure 4). However, simple effects analyses indicated significant difference in Hits in the Abstinent versus Non-abstinent sessions for Relapsers ($p < .05$), but not for Abstainers ($p > .05$). Subsequent Relapsers exhibited abstinence-induced declines in Hits, whereas the Abstainers did not.

For RVIP False Alarms, no significant Smoking Status by Visit Type interaction was observed (F [1, 189] = 0.034, $p > .05$, $\eta_p^2 = .000$). False Alarms were comparable at the Abstinent and Non-abstinent sessions for both Relapsers and Abstainers (p's > .05).

For Concentration Difficulty, a significant Smoking Status by Visit Type interaction was obtained (F [1, 185] = 5.18, $p < .05$, $\eta_p^2 = .027$; Figure 5). Simple effects analyses revealed a significant difference in Concentration Difficulty in the Abstinent versus Non-abstinent sessions for Relapsers ($p < .001$), but not for Abstainers ($p > .05$). Subsequent Relapsers exhibited abstinence-induced decrements in Concentration, whereas Abstainers did not.

For Summary Concentration Difficulty, a trend toward significant Smoking Status by Visit Type interaction was observed (F [1, 185] = 3.28, $p = .07$, $\eta_p^2 = .017$; Figure 6). Simple effects analyses indicated a significant difference in Summary Concentration Difficulty in the Abstinent versus Non-abstinent sessions for Relapsers ($p < .001$), but not for Abstainers ($p > .05$). Subsequent Relapsers exhibited abstinence-induced decrements in the Summary Concentration item, whereas Abstainers did not.

The second method utilized to evaluate the association between attention and subsequent smoking status was a series of hierarchical logistic regressions. In stage one, a multiple hierarchical logistic regression was conducted with Smoking Status as the outcome variable (Relapsed vs. Abstained) and attention difference scores as predictor variables. In the first block, Order and FTND were entered and in the second block, RVIP RT and RVIP Hits (difference scores) were entered simultaneously. The difference score of RVIP False Alarms was not entered because, as noted earlier, there was no significant abstinence-induced change in the number of false alarms. Stage one revealed that, controlling for nicotine dependence and order of visit type, the combination of RVIP RT and RVIP Hits (difference scores) explained significant variation in Smoking Status (X^2 [df = 2, N = 193] = 6.67, $p < .05$).

Stage two of these analyses involved a series of univariate hierarchical logistic regressions. Order of abstinence and FTND were included in the first block and attention difference scores (RVIP RT, RVIP Hits, RVIP False Alarms, Concentration Difficulty, and Summary Concentration Difficulty) were entered individually in a series of analyses for the second model. For these analyses, the predictors (difference scores) were standardized (M = 0, SD = 1) and reverse scaled for ease of interpretation of the odds ratios and to interpret based on the odds of relapse as opposed to the odds of remaining abstinent.

Controlling for FTND and order of visit type, RVIP RT difference scores significantly predicted subsequent Smoking Status (OR = 1.55, $p < .05$; Table 12). With every 1 SD increase in RVIP RT difference score, there was a 55% increase in the odds of relapse four weeks later. Likewise, Concentration Difficulty significantly predicted

succeeding Smoking Status (*OR* = 1.56, $p < .05$). With every 1 SD increase in Concentration Difficulty difference score, there was a 56% increase in the odds of relapse four weeks later. RVIP Hits (*OR* = 0.72, $p > .05$) and RVIP False Alarms (*OR* = 0.97, $p > .05$) did not significantly predict subsequent Smoking Status. While Summary Concentration Difficulty did not significantly predict subsequent Smoking Status, there was a trend toward significance (*OR* = 1.42, $p = .07$).

CHAPTER 5: Discussion

The present study investigated the association between abstinence-induced attention difficulties and subsequent smoking status in habitual smokers motivated to quit smoking. Clarification of the impact of withdrawal-related attention problems on smoking outcomes will help elucidate the cognitive processes underlying smoking relapse. Improving understanding of the relapse process can inform future treatment interventions.

EFFECT OF ACUTE ABSTINENCE ON ATTENTION

As expected, abstinence-induced attention difficulties were found using the RVIP task. Participants exhibited decreased accuracy and slower response times in the abstinent session compared to the non-abstinent session. The findings indicated small effect sizes, which is consistent with previous research (e.g., [62]).

However, acute nicotine abstinence did not influence commission errors (false alarms). Specifically, the number of false alarms made was comparable in the abstinent and non-abstinent sessions. In our sample, the range of false alarms made was minimal and very few participants made appreciable numbers of commission errors. This finding is also consistent with the literature. It is possible that although nicotine abstinence leads to attention declines, this diminished performance may not reflect clinical levels of deficit. It is plausible that the current relatively healthy sample of smokers did not exhibit clinical levels of attention deficits. "Relatively healthy" is defined here as the absence of severe psychopathology and an absence of in-patient hospitalizations for the duration of the study. Perhaps a sample exhibiting clinical levels of attention deficits will exhibit differences on false alarms between the abstinent and non-abstinent sessions.

McClernon and colleagues (65) found that smokers diagnosed with ADHD exhibited more false alarms than did non-ADHD smokers, using the Conners' CPT (Continuous Performance Test; a visual vigilance task). Another point of interest is that the RVIP task was also utilized in this study, however the same effects were not found on the task. This finding may suggest that the RVIP task is not sensitive to detect changes in false alarms. Overall, these findings suggest that nicotine abstinence in habitual smokers was associated with declines in sustained attention and working memory performance.

Consistent with the study predictions, abstinence-induced self-reported concentration difficulties were found. The findings reflected medium sized effects, which are consistent with the literature (e.g., [62]). Having consistent effect sizes across studies provide additional support for the findings and increase confidence in the data. These findings suggest that nicotine deprivation in habitual smokers reduces concentration abilities, as assessed by self-report.

Association between Objective and Subjective Attention Measures

Results also revealed an overall absence of correlations between subjective and objective measures, which is also consistent with past research. There are a number of possible explanations for this negative (null) finding. It may be the case that these are orthogonal processes, which are distinct aspects of attention that separately predict relapse. First, the RVIP indices may be distinctly dissociable from concentration ability. Conventionally, Correct Hits is a proxy for accuracy, Response Time reflects processing speed, and False Alarms indicate impulsivity. Concentration is a basic cognitive function that is clearly different from the aforementioned processes. Although concentration is necessary for other higher order cognitive processes, it is not a criterion that it be

correlated with the various cognitive domains. Along the same vein, because of the low specificity (given its relation to essentially all other cognitive domains) it may not correlate with the RVIP indices because it may not be sensitive or similar enough to them. To this end, it would be interesting to explore if any associations are found between variability of reaction time and the concentration subscale because increased variability reflect inattention and is consistently found to distinguish children diagnosed with ADHD (e.g., [10, 54]).

On a separate note, it is not uncommon to find an absence of concordance between subjective and objective indices of similar constructs (e.g., [39]). Indeed, studies across different fields consistently observed an absence of correlations (e.g., [24, 64, 68, 86]). Furthermore, many errors (explicit and/or implicit) occur when making subjective reports. Self-reports are susceptible to a number of biases, such as social desirability (51) and reasoning based on emotions (51, 88). Social desirability can result in under- or over-reporting, depending on the nature of the response and the potential consequences of such responses. Furthermore, the emotional state an individual is in while responding to a questionnaire can alter their report. Subjective reports are more prone to biases and this may contribute to the discrepant correlations with objective measures.

While RVIP indices and the WSWS concentration subscale items separately and directly predict smoking status, it is also possible that there is a third variable (or set of variables) that correlates with RVIP and WSWS in such a way that the association between these variables is attenuated. In other words, there might be a “true correlation”

between these two measures that is not visible in this study due to the influence of other variables that were not assessed.

Association between Attention and Subsequent Smoking

Results also revealed that abstinence-induced attention decrements predicted smoking status four weeks post quit day. These results may reflect the effect of withdrawal severity. Experiencing more severe withdrawal during abstinence may result in worse outcomes. Indeed, subsequent relapsers exhibited consistently worse performance during the abstinent session relative to the non-abstinent session. Future studies may consider formally testing this possibility by evaluating physiological, psychological, and cognitive withdrawal symptoms. Furthermore, subsequent relapsers were heavier smokers and had more nicotine in their system during the Non-abstinent session, as assessed by saliva cotinine levels. As such, it is possible that the heavier nicotine intake may cause worse withdrawal symptoms during deprivation, which would suggest the potential effect of withdrawal severity.

Alternatively, these findings may be attributable to the differential effect of nicotine sensitivity. Specifically, relapsers may be more susceptible to the effects of nicotine relative to abstainers. In fact, relapsers reported experiencing more of the beneficial effects of nicotine when smoking as usual (e.g., improved concentration) as well as detrimental effects of nicotine deprivation, evidenced by worse concentration during abstinence, compared to abstainers.

Cognitive resiliency may also be a contributing factor. It is plausible that protection from the detrimental effects of nicotine withdrawal during abstinence may lead to better outcomes. Support for this interpretation is provided by the abstainers'

consistent better performance during the abstinent as opposed to the non-abstinent sessions. Protective effects may be accomplished with the use of compensatory strategies that overcome abstinence effects. It is well known that higher intellectual ability can function as a protective factor (e.g., [18, 90]). In the present study, abstainers had significantly higher IQ scores compared to the relapsers.

The notion of poor sustained attention, indicated by attention lapses, leading to relapse is consistent with ideas that were proposed by various researchers in the field (e.g., [20, 66, 111]). However, an integrated formalized conception of this idea has yet to be developed. The current findings lend support to integrate the literature to this end with the hopes of unifying a model of the relationship between attention difficulties and relapse.

Although there was an absence of correlations between RVIP and WSWS items and the mechanisms underlying the relationship between abstinence-induced attention problems and future smoking status is undetermined, there are some clinical implications. The data revealed that abstinence-induced attention difficulties predict future lapses. Accordingly, these objective and subjective measures may inform treatment interventions to improve smoking cessation programs. It may the case that these individuals benefit from a single different treatment approach altogether and/or perhaps a dynamic intervention program that parallels the withdrawal timecourse. For instance, interventions could involve cognitive remediation to bolster these attention decrements at the outset. Alternatively, perhaps interventions that require less reliance on cognitive functions during acute withdrawal (such as behavioral approaches) then subsequently move to cognitive-based treatment during the later stages of abstinence (such as

cognitive-based psychotherapy) is warranted. Future studies may seek to clarify the underlying mechanisms in efforts toward refining our understanding of the underlying cognitive factors leading to relapse.

LIMITATIONS

There are some limitations of the present study that warrant consideration when interpreting these results. First, given the 25% attrition rate since the orientation visit, there is concern of potential selection bias. Such a self-selecting sample would indicate non-random sampling that can also limit generalizability, for instance to participants who can withstand lab protocols. However, this proportion is not uncommon. In another prospective smoking cessation study, approximately 35% of the sample dropped out of the study or failed to achieve 24 hours of abstinence (99). The subjects who prematurely dropped out of the present study were significantly different from the subjects who attended the quit day session with respect to general demographic information and smoking characteristics. The drop-outs were younger, poorer, and had smoked for fewer years (c.f., [7, 25, 32, 47, 48, 60, 62]). They also had lower IQ, suggesting that poor cognitive ability is a risk factor for dropping out. This latter finding may be clinically important in that individuals with poorer cognitive ability may need different treatments to prevent drop-out. It may also be the case that the study parameters served to filter out subjects who were not seriously motivated or committed to quit smoking. Consequently, the remaining sample may reflect a sample of smokers more ready to quit smoking.

Another limitation was that the study was not designed to assess for or exclude based on neurological disorders, caffeine use, medications, or vision problems. The effects from these factors could have potentially confounded the cognitive findings.

Furthermore, the outcome measure was operationalized as point prevalence smoking status. This definition limits differentiating temporary lapses from true relapse (c.f., [79]). However, research suggests that relapse risk is highest within ten days and lapses robustly predict eventual relapse (33, 45, 79). As such, the study's timeline provides some indirect support for relapse.

Ceiling effects for RVIP hits were demonstrated as a number of subjects obtained the maximum number of hits. A higher ceiling, by way of more targets or longer task duration, may function to increase the variability in scores and may improve the ability to detect significant interactions. This pattern of findings suggests that RT may be a more sensitive index for relapse prediction with the current short (6 minute) version of the RVIP task (compared to the traditionally lengthier 10-12 minute task). Another limitation was that we were unable to extract a measure of RT variability on the RVIP task. This is a priority for future research.

STRENGTHS

Some strengths of the present study include the prospective study design, which enables delineation of the temporal relationship of variables and bypasses biases of retrospective designs. Further, the longitudinal design permits tracking changes over time and bypasses limitations from cross-sectional designs. This type of study design provides more confidence to suggest cause-effect relationships. The experimental manipulation of abstinence further increased confidence that the effects were due to nicotine deprivation, using a within-subject design. Moreover, employing such a design served to limit extraneous between-subjects differences, as each person served as their own control. Additionally, smoking was verified with objective biomarkers. This

approach enabled less reliance on self-reports that can be wrought with biases, such as recall and response biases. Counterbalancing visit type (the abstinent and non-abstinent sessions) as well as the RVIP and WSWS subscale limited extraneous confounds such as order effects. Furthermore, the primary measures were also yoked to capture present moment attention capabilities.

The study was ecologically valid in that the population assessed was habitual smokers motivated to quit. Similarly, withdrawal (abstinent session) and chronic effects (non-abstinent session) of smoking were captured. These are states that current smokers planning to quit would experience. Lastly, this study is the first to link abstinence-induced attention detriments to clinical outcomes, thereby providing valuable novel information to inform future treatment interventions.

IMPLICATIONS AND FUTURE DIRECTIONS

There are several clinical implications of these findings. The RVIP and WSWS measures could be used to identify individuals most at risk of early relapse. The greater magnitude of effect for the self-report items suggests that these items may yield greater practical significance relative to the RVIP indices. Furthermore, the findings suggest that RVIP RT may be a more sensitive index than Hits in predicting relapse. Also, the significant findings with this abbreviated version of the RVIP task lend themselves to practicality and functionality in clinical settings, compared to the traditionally longer tasks. Subsequently, interventions targeted at improving working memory and sustained attention (e.g., cognitive remediation; [42]) may be a promising avenue toward improving smoking cessation efforts.

Future directions could investigate the trajectory and duration of attention difficulties beyond withdrawal effects, given that withdrawal symptoms are known to subside within four weeks (e.g., [41, 97]). This information would enable a more comprehensive understanding of the nature of this phenomenon. Having this knowledge would help determine the scope of future interventions. It may be the case that interventions targeting sustained attention and working memory are more useful earlier on, while interventions at later time points are better suited to target other factors (such as smoking temptations) that promote relapse. Furthermore, by evaluating attention changes using an ecological momentary assessment paradigm, ecologically valid and rich data on the nature of attention difficulties may be obtained. This approach, in turn, would enable a fine-grained understanding of this phenomenon. For instance, this method would enable an examination of precisely what types of withdrawal symptoms (and when they occur) that influence relapse.

Table 1. Summary of studies investigating the role of nicotine on RVIP performance in humans.

Study	Population	Nicotine Conditions	Blinding	Acute Nicotine vs. Acute Abstinence	Administration Route	Primary Independent Variables (Task[s])	Primary Outcome Variables (Task[s])	RVIP Findings	Notes
Wesnes & Warburton (1983)	Experiment 1: *N*=24 male undergrad smokers. Experiment 2: *N*=12 male and female undergrad smokers	Exp1: cigarettes 0.28 (Con), 0.71, 1.65 mg nicotine. Exp2: nicotine-free (Con), 0.60, & 1.84 mg nicotine	Unspecified	Acute nicotine	Cigarette	Condition; Time	RIPT (Hits, RT, Omission errors)	**Nicotine improved RIPT performance** (decreased RT & increased Hits), relative to baseline. Exp1: greatest improvements with highest nicotine and tar cig. Exp2: performance worse over time with no to less nicotine.	Two Experiments (only males in expt1 and both sexes in epxt2)
Edwards, et al. (1985)	*N*=19 male undergrad smokers	No smoking, 0.9, 1.5mg nicotine cig	Unspecified	Acute nicotine	Cigarette	Condition	RVIP (Hits, RT, Omission errors)	**Acute nicotine improved RVIP** performance (increased Hits & decreased RT), relative to baseline smoking and 12-hr deprivation; no trade-offs b/w RT and Hits.	ERP recording
Petrie & Deary (1989)	*N*=12 smokers	Smoking vs. No-smoking	Unblind	Acute nicotine	Cigarette	Condition; Task trials	RVIP (Hits, RT, False Alarms)	**Acute nicotine improved RVIP**. Only RT decreased, during first 5mins of task (not Hits or FA).	Other cognitive tasks (digit symbol substitution test, inspection time test)

Parrott & Craig (1992)	*N*=16 smokers	placebo gum, 2mg nicotine gum, 4mg nictotine gum, cigarette smoking (own brand; all low/medium nicotine)	Double-blind	Acute nicotine	Nicotine gum & cigarette	Condition; Time	RVIP (Hits, RT, False Alarms)	**Acute nicotine improved RVP performance** (decreased RT & increased Hits) compared to placebo.	Monotonic dose-response for Hits at post-test 1. Curvilinear dose response effect (inverted U) for Hits and RT at post-test 2. Other cognitive tasks.
Foulds et al. (1996)	*n*=18 Abstainers & *n*=18 Never smokers	Abstainers vs. Never-smokers; 0.3mg nicotine x2, 0.6mg nicotine x2, saline placebo	Double-blind	Acute nicotine	Subcutaneous injection	Condition; Time	RVIP (Hits, RT, sensitivity)	**Acute nicotine improved RVP performance.** For abstinent smokers: increased hits, shorter RT, increased sensitivity. For never-smokers: shorter RT.	Other cognitive tasks

Herbert et al. (2001)	*N*=45 College & staff smokers	Ad lib smoking before testing (55% smoked within 30mins & 2 Ss didn't smoke for 10+hrs) vs. "Abstinent"; distraction (music video)	Unblind	Acute nicotine	Cigarette	Condition; Time	RVIP (Hits, RT, False Alarms)	**Acute nicotine didn't improve RVIP** performance in non-deprived smokers.	Mood measures
File et al. (2001)	*n*=16 nicotine condition & *n*=16 placebo condition; never-smoking med students	Nicotine inhaler vs. Placebo inhaler	Double-blind	Acute nicotine	Nicorette inhalator	Condition; Time; Gender	RVIP (Hits, RT)	**Acute nicotine had no effect on RVIP** on never-smokers, although there was a ns trend of increased Hits.	All Ss never-smoking Medical students. No control or comparison groups (all were never-smoking med students). Other cognitive and mood measures.
Lawrence et al. (2002)	*n*=15 smokers & *n*=15 non-smokers	Nicotine vs. Placebo	Unblind	Acute nicotine	Transder mal patch	Condition; Smoking status; Order of nicotine	RVIP (Hits, RT, False Alarms)	**Acute nicotine improved RVIP performance** (increased accuracy and decreased RT).	fMRI, mood measures
Poltavski & Petros (2005)	*N*=47 College Males; *n*=25 Smokers (*M*=13 cig/day) & *n*=22 Non-smokers	Smokers vs. Non-smokers; Nicotine patch vs. Placebo patch	Double-blind	Acute nicotine & acute abstinence	Transder mal patch	Condition; Time	RVIP (Hits, RT)	**No group differences on RVIP** (never-smokers = smokers in placebo or nicotine condition) - no acute nicotine or acute abstinence.	Other cognitive & physiological measures

Hendricks et al. (2006)	*N*= 50 Smokers	Abstainers vs. Ad-lib Smokers	Unblind	Acute abstinence	N/A	Condition; Time	RVIP (RT, Omission and Commission errors)	**Acute abstinence impaired RVIP performance (**decreased RT within 30mins. of deprivation).	No effects found for RVIP omission errors and FA. Withdrawal measures (e.g., WSWS).
Kelemen & Fulton (2008)	*N*=41 "Moderate" College smokers	Abstinent vs. Non-abstinent sessions; Nicotine gum vs. Placebo gum	Double-blind	Acute nicotine & acute abstinence	Nicotine gum	Condition	RVIP (Hits, RT, False Alarms)	**Acute nicotine improved RVIP performance** (increased hit rate but no increase in false alarms). **For 8-hr abstainers nicotine associated with poor sustained attn** (decreased Hits & increased RT).	Other cognitive tasks
Rusted & Alvares (2008)	*N*=48 Never-smokers college students	Nicotine nasal spray vs. Placebo nasal spray	Double-blind	Acute nicotine	Nasal spray	Condition; Stress (low, high)	RVIP (Hits, RT, False Alarms)	**Nicotine improved RVIP performance.** (Decreased RT compared to placebo in never-smokers. No effects on Hits or FA.	Other cognitive, mood, physiological measures
Leventhal et al. (2010)	*N*=203 smokers not attempting to quit.	Abstinent vs. Non-abstinent (ad-lib smoking) sessions	Unblind	Acute abstinence	N/A	Condition	RIPT (Hits, RT, False Alarms)	**Acute abstinence impaired RIPT performance** (delayed RT & decreased hit rate).	Subjective, other cognitive, mood, & physiological measures
Juliano et al. (2011)	*N*=148 smokers	Nicotine cig vs. Placebo cig	Balanced placebo design	Acute nicotine	Cigarette	Condition; Expectancy (told placebo vs. told cig)	RVIP (RT, Hits, sensitivity)	**Nicotine improved RVIP performance.** Increased Hits, decreased RT, & increased Sensitivity. Expectancy effect of dose for False Alarms (increased FA with placebo instructions compared to nicotine instructions=people expected to do worse and did worse if placebo).	Mood

Nesic et al. (2011)	*N*=48 smokers	Non-abstinence vs. Abstinence		Acute nicotine	Cigarette	Condition; Time; Nicotine Dependence Level (low, high)	RVIP (Hits, RT, False Alarms)	**No effects on RVIP, but likely due to practice effects** (administered 4xs within single day); improvements found across administrations for Hits, FA, and RT. However, less improvement found in the high nicotine dependent group, relative to low dependent (suggesting reduced plasticity [ie, practice effects] in higher dependents).	Other cognitive & mood measures.

Table 2. Internal reliability: Cronbach's alphas for Concentration Difficulty self-report items by Visit Type.

Subscale	Cronbach's α	Internal Reliability	No. of items
Concentration Difficulty (Ab)	0.897	Excellent	3
Concentration Difficulty (Non)	0.842	Good	3

Note. n = 189. Ab=Abstinent session; Non=Non-abstinent session.

Table 3. Concurrent validity: Pearson's correlations between Concentration Difficulty and Marker items by Visit Type.

Concentration Difficulty	Marker item (Non)	Marker item (Ab)
Item_1 (Non)	.572**	.264**
Item_1 (Ab)	.364**	.751**
Item_2 (Non)	.713**	.334**
Item_2 (Ab)	.330**	.720**
Item_3 (Non)	.637**	.307**
Item_3 (Ab)	.331**	.812**

Note. $n = 189$, $^{**}p < .01$. Ab=Abstinent session; Non=Non-abstinent session.

Table 4. Demographic information for participants who attended Quit Day and had valid RVIP data (*N*=193).

	M (%)	*SD*
Sex (% Male)	55.4	
Race (% White)	54.9	
Age in years	43.98	11.79
FTND	5.15	2.02
Time to first cigarette[a]	2.17	0.77
Cigarettes/Day	19.5	8.27
Baseline CO level (ppm)	21.05	10.07
Cotinine levels in saliva (ng/ml)	385.16	223.7
Years smoked	24.15	11.96
Past quit attempts	5.30	3.10
Shipley IQ	104.41	10.78
Education completed in years	14.25	2.2
Annual family income[b]	5.2	3.36
Site (% USU)	42.0	

Note. RVIP=Rapid Visual Information Processing task; USU=Uniformed Services University of the Health Sciences. [a]FTND Item 1: Time to the first cigarette of the day (0=after 1hr; 1=31-60mins; 2=6-30mins; 3=within 5mins), [b]Income before taxes (4=$30,000-$39,999; 5=$40,000-$49,999; 6=$50,000-$59,999). *N*'s = 193 except Shipley IQ (*n*=192), Years of education (*n*=191), and Cotinine levels in saliva (*n*=191).

Table 5. Demographic information for participants who attended Quit Day and had valid RVIP data for USU site (*n*=81).

	M (%)	*SD*
Sex (% Male)	64.2	
Race (% White)	42.0	
Age in years	45.11	10.99
FTND	5.14	1.83
Time to first cigarette[a]	2.23	0.77
Cigarettes/Day	18.86	8.14
Baseline CO level (ppm)	18.47	7.28
Cotinine levels in saliva (ng/ml)	446.95	267.49
Years smoked	25.96	11.72
Past quit attempts	5.31	3.07
Shipley IQ	102.64	11.59
Education completed in years	14.12	2.13
Annual family income[b]	4.53	3.35

Note. RVIP=Rapid Visual Information Processing task; USU=Uniformed Services University of the Health Sciences. [a]FTND Item 1: Time to the first cigarette of the day (0=after 1hr; 1=31-60mins; 2=6-30mins; 3=within 5mins), [b]Income before taxes (4=$30,000-$39,999; 5=$40,000-$49,999; 6=$50,000-$59,999). *N*'s = 193 except Shipley IQ (*n*=192), Years of education (*n*=191), and Cotinine levels in saliva (*n*=191).

Table 6. Demographic information for participants who attended Quit Day and had valid RVIP data for MDACC site (*n*=112).

	M (%)	*SD*
Sex (% Male)	49.1	
Race (% White)	64.3	
Age in years	44.63	11.69
FTND	5.11	2.20
Time to first cigarette[a]	2.11	0.81
Cigarettes/Day	20.02	8.68
Baseline CO level (ppm)	22.37	11.36
Cotinine levels in saliva (ng/ml)	339.08	186.90
Years smoked	24.40	11.80
Past quit attempts	5.49	3.13
Shipley IQ	105.30	10.47
Education completed in years	14.35	2.25
Annual family income[b]	5.80	3.28

Note. RVIP=Rapid Visual Information Processing task; USU=Uniformed Services University of the Health Sciences. [a]FTND Item 1: Time to the first cigarette of the day (0=after 1hr; 1=31-60mins; 2=6-30mins; 3=within 5mins), [b]Income before taxes (4=$30,000-$39,999; 5=$40,000-$49,999; 6=$50,000-$59,999). *N*'s = 193 except Shipley IQ (*n*=192), Years of education (*n*=191), and Cotinine levels in saliva (*n*=191).

Table 7. Paired samples t-test results for attention variables by Visit Type with means and standard deviations.

	Abstinent Session	Non-Abstinent Session			
	M (SD)	*M (SD)*	*t-value*	*p*	*Cohen's d*
RVIP Hits (0-27)	18.58 (4.51)	19.26 (4.84)	2.00	.04	0.14
RVIP RT (ms)	432.73 (97.67)	416.43 (82.34)	-2.46	.01	0.18
RVIP FA (0-273)	3.72 (11.35)	3.91 (12.48)	-0.27	.79	0.02
Concentration Difficulty (0-4)	1.65 (1.02)	1.16 (0.76)	6.43	<.001	0.47
Summary Score (0-10)	3.65 (2.84)	2.33 (2.35)	6.48	<.001	0.47

Note. RVIP=Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. RVIP RT, RVIP Hits, RVIP FA (*n* = 193); Difficulty Concentrating, Summary Score (*n* = 189).

Table 8. Pearson's correlations and 95% confidence intervals using absolute values of RVIP and Concentration Difficulty indices at the Abstinent session.

Subscale	RVIP Hits	RVIP RT	RVIP FA
Concentration Difficulty	.03 [-.11, .17]	-.14 [-.28, .00]	-.12 [-.26, .02]
Summary Score	.02 [-.12, .16]	-.08 [-.22, .06]	-.08 [-.22, .06]

Note. RVIP= Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. Data are Pearson's *r* values with [95% CI]; all *n*'s = 189.

Table 9. Pearson's correlations and 95% confidence intervals using absolute values of RVIP and Concentration Difficulty indices at the Non-abstinent session.

Subscale	RVIP Hits	RVIP RT	RVIP FA
Concentration Difficulty	.11 [-.03, .25]	-.12 [-.26, .02]	-.04 [-.18, .10]
Summary Score	.05 [-.09, .19]	-.11 [-.25, .03]	.01 [-.13, .15]

Note. RVIP= Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. Data are Pearson's *r* values with [95% CI]; all *n*'s = 189.

Table 10. Pearson's correlations and 95% confidence intervals using difference scores for RVIP and Concentration Difficulty indices.

Subscale	RVIP Hits	RVIP RT	RVIP FA
Concentration Difficulty	-.04 [-.18, .10]	.05 [-.09, .19]	.04 [-.10, .18]
Summary Score	.01 [-.13, .15]	.04 [-.10, .18]	.07 [-.07, .21]

Note. RVIP= Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. Data are Pearson's *r* values with [95% CI]; all *n*'s = 189.

Table 11. Simple effects analyses for attention variables for Abstainers and Relapsers with means and standard deviations by Visit Type.

	Abstainers			Relapsers		
	Abstinent	Non-Abstinent		Abstinent	Non-Abstinent	
	M (SD)	*M (SD)*	*p*	*M (SD)*	*M (SD)*	*p*
RVIP Hits (0-27) [a]	19.58 (4.33)	19.24 (5.46)	.63	18.34 (4.53)	19.26 (4.69)	.01
RVIP RT (ms) [a]	416.55 (89.17)	428.11 (89.63)	.45	436.69 (99.51)	413.57 (80.51)	.001
RVIP FA (0-273) [a]	1.68 (2.70)	1.63 (2.12)	.96	4.21 (12.55)	4.47 (13.84)	.75
Concentration Difficulty (0-4) [b]	1.50 (0.94)	1.36 (0.80)	.43	1.68 (1.04)	1.11 (0.75)	<.001
Summary Score (0-10) [b]	3.19 (2.76)	2.59 (2.34)	.23	3.76 (2.85)	2.26 (2.36)	<.001

Note. RVIP= Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. [a] *n*=38 Abstainers, *n*=155 Relapsers; [b] *n*=37 Abstainers, *n*=152 Relapsers

Table 12. Hierarchical logistic regressions results for subsequent smoking status.

Attention Variable	*OR*	95% *CI*	*p*
RVIP Hits [a]	1.55	1.03, 2.34	.04
RVIP RT [a]	0.72	0.48, 1.08	.11
RVIP FA [a]	0.97	0.67, 1.39	.85
Concentration Difficulty [b]	1.56	1.05, 2.31	.03
Summary Score [b]	1.42	0.97, 2.08	.07

Note. RVIP= Rapid Visual Information Processing task; RT=reaction time; FA=false alarm. *OR*=odds ratio; *CI*=confidence interval; RT=reaction time; FA=false alarms; CD=concentration difficulty. Odds ratios were computed using standardized predictor variables. *OR*s are adjusted for FTND and order of abstinence session. [a]*n*=38 Abstainers, *n*=155 Relapsers; [b]*n*=37 Abstainers, *n*=152 Relapsers.

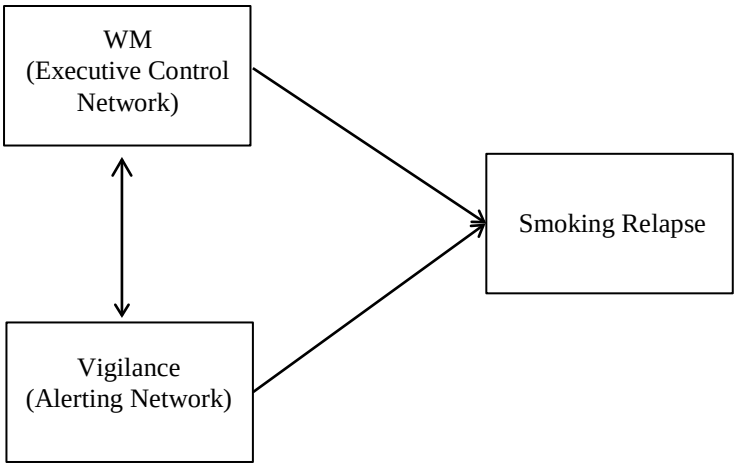

Figure 1. Conceptual model. WM = Working memory.

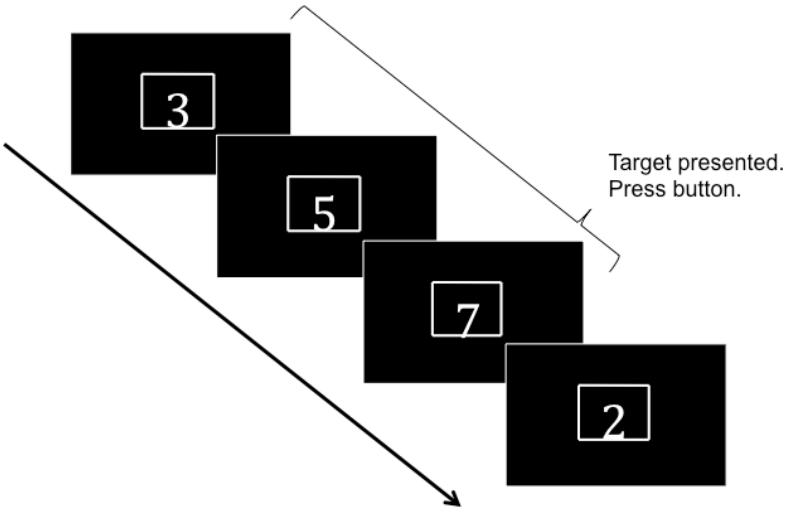

Figure 2. Sample serial presentation of the Rapid Visual Information Processing task.

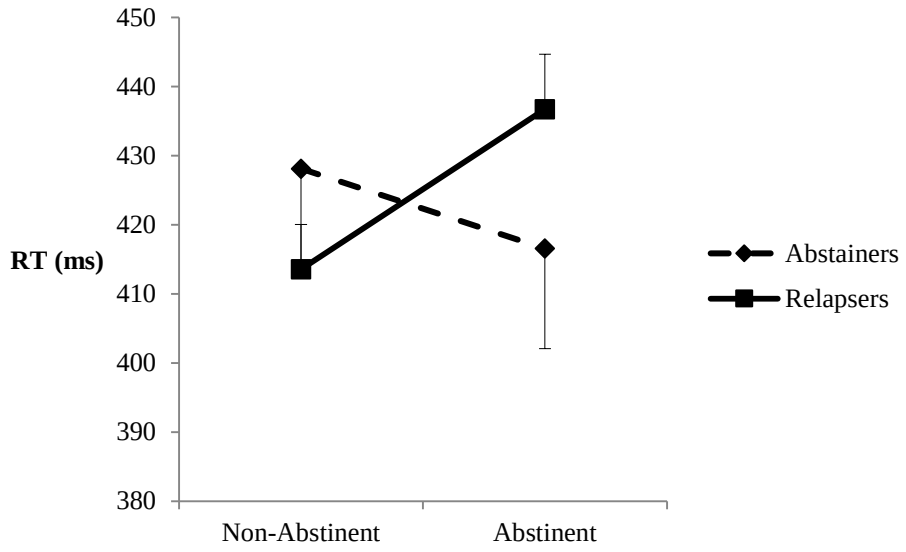

Figure 3. RVIP RT: Smoking Status by Visit Type. Rapid Visual Information Processing task mean Reaction Time was the time it took the subject to make an accurate response, measured in milliseconds; larger values indicate poorer performance. Error bars are ±1SE.

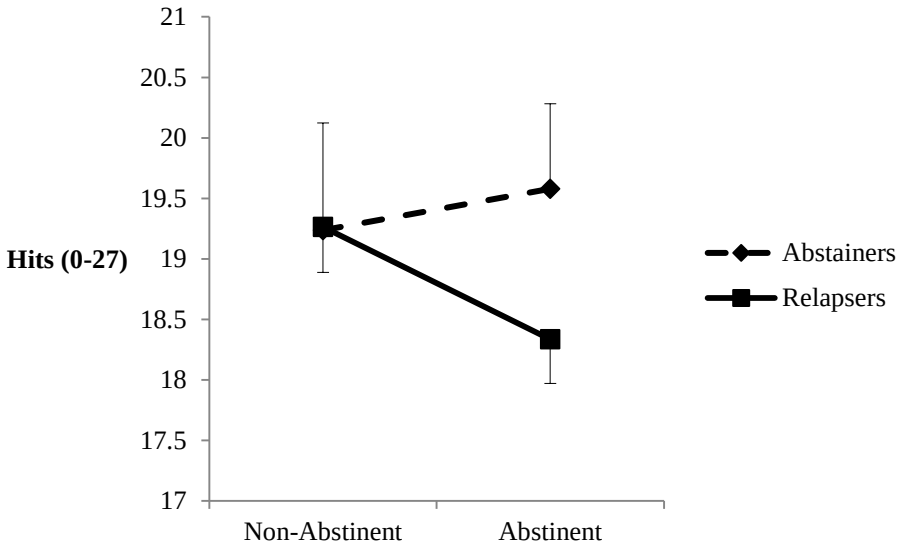

Figure 4. RVIP Hits: Smoking Status by Visit Type. Rapid Visual Information Processing task Hits ranged from 0 to 27; larger values indicate better performance. Error bars are ±1SE.

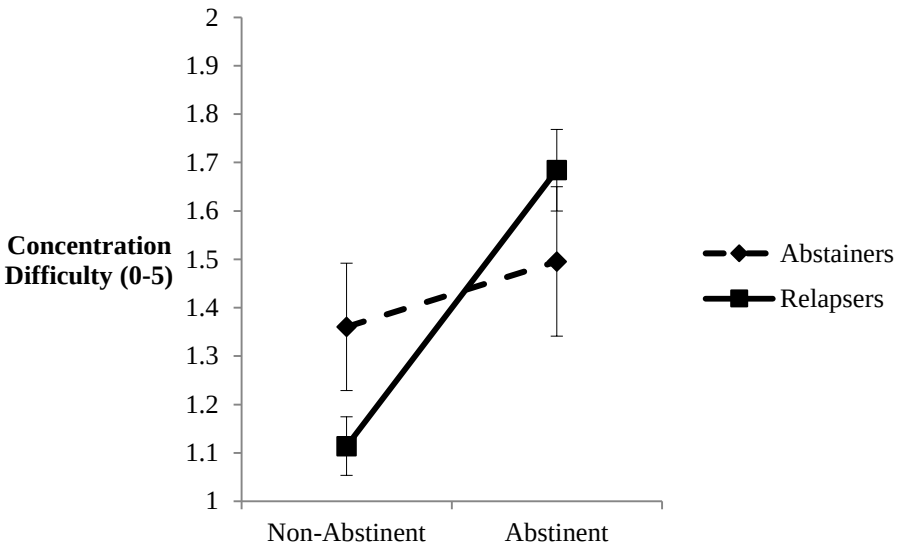

Figure 5. Concentration Difficulty: Smoking Status by Visit Type. The Concentration Difficulty subscale from the Wisconsin Smoking Withdrawal Scale ranged from 0 to 5; larger values indicate poorer concentration. Error bars are ±1SE.

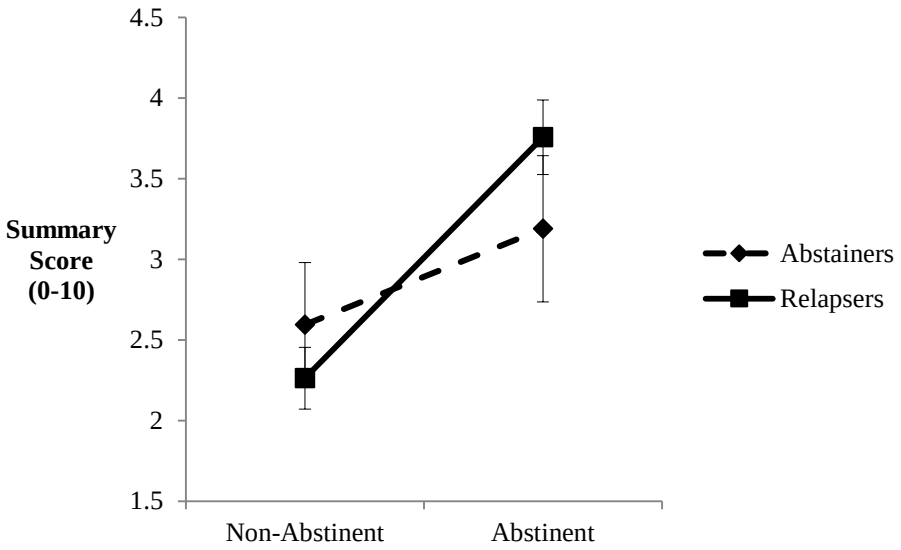

Figure 6. Summary Concentration Difficulty: Smoking Status by Visit Type. The Summary Concentration score ranged from 0 to 10; larger values indicate poorer concentration. Error bars are ±1SE.

APPENDIX A: Rapid Visual Information Processing Task Standardized Instructions

RVIP standardized task instructions. Subjects were instructed to use the index finger of their dominant hand to press the external press pad. At the outset of the training session, subjects were given these instructions.

"You are going to see some numbers appearing one at a time in a box in the center of the computer screen. What you have to do is to look for a target sequence of three numbers and press the button whenever you spot the target.

The target sequence will be a '3' immediately followed by a '5', immediately followed by a '7'. It is only when you see the last number of the sequence that you should press the button.

Full prompts will be provided.

To begin, you will know that a sequence has begun because the target sequence will appear in red and be underlined in yellow. There will also be a 'beeping' sound if you press the button correctly. As the practice sequence progresses you will find that these cues and the 'beeping' sound will gradually be phased out."

If the subject responds too early, the test administrator prompts the subject to "Wait until you see the last digit before pressing the button."

The subject will next be informed that some prompts will be provided: "Now the sequences will only be underlined in yellow."

Next, the subject will be informed that no prompts will be provided: "Now you will have to spot the sequences yourself. There will be no underlining or beeping."

Upon completion of the training trials, the test trials will commence with the following instructions:

"This time we will do the same thing, but there will now be two other sequences you have to remember, 2-4-6 and 4-6-8 as well as 3-5-7.

Whenever you see any of these three target sequences you should press the button when the third digit appears. The test will last for four minutes, so please try to concentrate until the end. The target sequences will remain on the screen to help you remember them. However, try to concentrate on the box in which the umbers are changing. Please respond as quickly as you can whilst trying to avoid making mistakes. Take a few seconds to familiarize yourself with the three different sequences, 3-5-7, 2-4-6, and 4-6-8. Remember there will be no color, no underlining, and no beeping sound."

APPENDIX B: Uniformed Services University of the Health Sciences Institutional Review Board Approval

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

September 8, 2009

MEMORANDUM FOR DR. ANDREW WATERS, PH.D., MEDICAL AND CLINICAL PSYCHOLOGY

SUBJECT: Uniformed Services University Institutional Review Board (FWA 00001628; DoD Assurance P60001) Approval regarding Human Subjects Research Protocol G172JY.

Congratulations! The amendment for your No More Than Minimal Risk human subjects research protocol G172JY, entitled "*Cognitive Processes in Smoking Cessation,*" was reviewed and approved for execution on Tuesday, September 8, 2009 by Edmund G. Howe III, M.D., J.D., Chairperson, Uniformed Services University IRB, under the provisions of 32 CFR 219.110(b)(2). This approval will be reported to the full Uniformed Services University IRB scheduled to meet on Thursday, October 15, 2009.

The purpose of this behavioral research study is to find out which types of smokers are in need of more help with quitting smoking.

This action approves amendment #5 that: (1) adds two study personnel (CITI complete 7/18/09 and 8/13/09); (2) revises recruitment numbers up to 250 to account for participants who sign the ICD but are later deemed ineligible; (3) makes minor revisions to the ICD regarding compensation; and (4) adds venues for study advertisements (utilizing the previously approved advertisements).

Authorization to conduct protocol G172JY will automatically terminate on Tuesday, January 5, 2010. You are authorized to enroll up to 250 subjects in this study. If you plan to continue data collection or analysis beyond this date, IRB approval for continuation is required. Please submit a USU Form 3204A/B (application for continuing approval) to the IRB Office 60 days prior to the termination date. The IRB Office will attempt to assist you by sending you a reminder; however, submission of an application for continuation is your responsibility. Please note the termination date and the date for submission of your USU Form 3204A/B in your calendar!

You are required to submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project to this office for review. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding this IRB action, or questions of a more general nature concerning human participation in research, please contact the undersigned at mstretch@usuhs.mil or (301) 295-0819.

[redacted]

Micah Stretch, M.A., J.D.
IRB Coordinator

cc: Chair, MPS
VPR/OSP
✓ File

APPENDIX C: The University of Texas M.D. Anderson Cancer Center Approval of Data Transfer

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1437
Phone 713-792-2933
Fax 713-794-4589

To: Paul Cinciripini 03/31/2009
From: Marion B. Olson
CC: Sunetra Martinez, Victoria L. Brown, Evanna L. Thompson, Veronica Roberts
MDACC Protocol ID #: 2005-0741
Protocol Title: Cognitive Processes in Smoking Cessation
Version: 13

Subject: Administrative IRB Approval – Protocol 2005-0741

On Tuesday, 03/31/2009, the Institutional Review Board (IRB) 4 chair or designee reviewed and approved your revision dated 03/27/2009 for Protocol 2005-0741

These Pages Include:

- Protocol Body – Document header Date: 03/27/2009

Revision included the following changes:
Clarifying that the de-identified data will be sent to Dr. Andrew Waters and his statistical team at the Uniformed Services University of the Health Sciences.

Additional Revision History:
Please note that along with this revision the M. D. Anderson IRB approves the transfer of de-identified study data for analysis to Dr. Andrew Waters, collaborator on this study, and his statistical team at the Uniformed Services University of the Health Sciences.

The revision can now be implemented. Please inform the appropriate individuals in your department or section and the collaborators of these changes.

Please inform the appropriate individuals in your department/section and your collaborators of these revisions.

Please Note: This approval does not alter or otherwise change the continuing review date of this protocol.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Marion B. Olson 03/31/2009 10:02:17 AM

This is a representation of an electronic record that was signed electronically and below is the manifestation of that electronic signature:

Marion B. Olson
03/31/2009 09:51:14 AM

IRB 4 Chair Designee
FWA #: IRB 4 IRB00005015

APPENDIX D: USUHS Informed Consent Form

This consent form is valid only if it contains the IRB stamped date

Consent for Voluntary Participation in a Non-Clinical Research Study

1. INTRODUCTION OF THE STUDY

You are being asked to be in a research study entitled, "Cognitive Processes in Smoking Cessation", at the Uniformed Services University (USU), Bethesda, Maryland. You have been asked to take part in this study because you are a smoker, and you want to quit smoking. Your participation is voluntary. Refusal to participate will not result in any punishment or loss of benefits to which you are otherwise permitted. Please read the information below, and ask questions about anything you do not understand, before deciding whether to take part in the study.

2. PURPOSE OF THE STUDY

The purpose of this behavioral research study is to find out which type of smokers are in need of more help with quitting smoking. This study may help researchers create more effective cessation (quitting) programs. Researchers want to learn the reasons why some smokers who quit smoking choose to start up again (relapse) more quickly than other smokers. Also, researchers want to use computerized tasks to help predict who is likely to relapse.

Other studies have shown that some computerized tasks are helpful in determining which smokers are likely to relapse more quickly. We want to carry out more research using additional tests.

3. PROCEDURES TO BE FOLLOWED

If you agree to be in this study, you will be asked to attend a total of 6 sessions at USU. At the first session (orientation), you will complete a breath test that allows the investigators to know how much you smoke. You will also complete about 7 questionnaires, which will take a total of about 1 hour to complete. The questionnaires will ask about you and your health, your smoking habits, and your drinking habits. There will also be a brief reading test, which will take about 5 minutes to complete. It will check your reading ability. The orientation will help researchers learn if you are eligible to participate in this study.

If you are found to be eligible and you wish to take part in this study, you will attend 5 laboratory sessions at USU. You will attend 2 sessions before trying to quit, 1 session on your quit day, 1 session one week after your quit day, and a final session 1 month after your quit day. At each of these laboratory sessions, you will complete a series of computerized evaluations, which will take about 90 minutes to complete. These evaluations are reaction-time tests.

At the 2 pre-quit sessions, you will be asked to smoke a cigarette (after the computerized evaluation). Before one of these pre-quit sessions, which will be picked randomly, you will be asked to stop smoking for 12 hours before the session.

During each of the laboratory sessions, you will also complete about 7 questionnaires that ask about your mood, cigarette cravings, and smoking habits. These questionnaires will take about 30 minutes in total to complete at each session. You will also be asked to complete a breath test and to provide a saliva sample. The breath test and the saliva sample will help the researchers find out how much you have smoked.

You will also be called on 2 occasions after your quit day, and you will be asked some questions about your smoking. Each phone call will last about 15 minutes. During the study, a staff member will meet with you for 10 to 20 minutes and help you to try and quit. You will meet with the staff member at each of the laboratory sessions. Every participant will receive the same help.

Some participants will be asked to carry a handheld computer (PDA) around for 1 week after their quit day. The PDA will beep randomly about 4 times a day (random assessments). Participants will answer some questions about their mood and craving, and complete a computerized reaction time task. Each assessment takes about 5 minutes.

Participation in this study will be over after your final visit to USU, which will be 4 weeks after your quit day.

4. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

Up to 250 subjects are expected to take part in this study at USU.

5. AMOUNT OF TIME FOR YOU TO COMPLETE THE STUDY

If you are eligible, you will be part of this study for about 7 weeks.

ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

Civilians and military personnel may be paid for participation in this study. Payments will be made after each visit, as described above.

Civilians (non-federal). You will receive $25 for completing the orientation (the first session). You will also receive $50 for completing each laboratory session. You will receive compensation after each session. You will also receive $15 for each telephone assessment that you complete, and you will receive this at the final laboratory session. Participants who carry around the PDA for a week will receive $2.50 for each random assessment that they complete.

Civilians (federal). You will only receive compensation for laboratory sessions/telephone assessments if those sessions occur during non-duty hours. In addition, if you wish to be compensated for participation during non-duty hours, you must file a request for outside activity. If

the request is approved and the sessions occur during non-duty hours, payment will be made as follows. You will receive $25 for completing the orientation (the first session). You will also receive $50 for completing each laboratory session. You will receive compensation after each session. You will also receive $15 for each telephone assessment that you complete (if those assessments occur during non-duty hours), and you will receive this at the final laboratory session. Federal civilians may participate in the PDA part of the study, but they can only be compensated for the PDA assessments that occur during non-duty hours.

Uniformed Personnel. You will only receive compensation for laboratory sessions if those sessions occur during non-duty hours. In addition, if you wish to be compensated for participation during non-duty hours, you must file a request for outside activity. If the request is approved and the sessions occur during non-duty hours, payment will be made as follows. You will receive $25 for completing the orientation (the first session). You will also receive $50 for completing each laboratory session. You will receive compensation after each session. You will also receive $15 for each telephone assessment that you complete (if those assessments occur during non-duty hours), and you will receive this at the final laboratory session. Uniformed personnel may participate in the PDA part of the

study, but they can only be compensated for the PDA assessments that occur during non-duty hours.

Please Note: Federal Civilians and Uniformed Personnel should inform their supervisors about the study for which they are volunteering whether or not they will receive compensation.

At the orientation session, if you are ineligible for the study because the breath test indicates that you have low levels of carbon monoxide in your breath, the orientation session will end right away and you will receive $10 for your time and travel expenses. If you are ineligible for another reason, the session will last for a longer duration and you will receive $25 for your time and travel expenses. Payments to ineligible participants follow the same rules as those written above for the eligible participants.

7. POSSIBLE RISKS OR DISCOMFORTS FROM BEING IN THIS STUDY

The expected risks or discomforts from being in this study are expected to be minimal. There are no known risks associated with the computerized evaluations. On 1 pre-quit session, you will arrive having not smoked on that day. You may experience symptoms of nicotine withdrawal, which include restlessness, difficulty concentrating, and/or mood changes. You will also smoke a cigarette at each of the pre-quit visits. Though smoking is considered bad for your health, your smoke intake is not likely to be increased by

participating in this study. (Your smoke intake is likely to be decreased by participating in the study).

You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaires, you are encouraged to contact your doctor or the study chair.

If something in this research makes you uncomfortable or upset, you may choose to stop taking part in this research at any time without loss of benefits; you may contact the investigator for referral. If the investigators note any distress or anxiety associated with the research, you will receive referrals, if appropriate.

POSSIBLE BENEFITS FROM BEING IN THIS STUDY

You may benefit from this study because if you are able to quit, this may be very beneficial to your health. Future smokers may benefit from what is learned. The information we learn may help us learn to develop better smoking cessation programs.

However, no benefit can be guaranteed.

9. CONFIDENTIALITY/PRIVACY AND HOW YOUR IDENTITY AND YOUR RESEARCH RECORDS WILL BE MAINTAINED

All information you provide as part of this study will be confidential and will be protected to the fullest extent provided by law. Your responses to our interviews and questionnaires, as well as audio-taped sessions will be maintained in a locked filing cabinet in lab offices in the Department of Medical and Clinical Psychology. All records related to this study will be accessible to those persons directly involved in conducting this study and members of the USUHS Institutional Review Board (IRB), which provide oversight for protection of human research volunteers. In addition, the IRB at USUHS and other federal agencies that help protect people who are involved in research studies, may need to see the information you give us. Other than those groups, records from this study will be kept private to the fullest extent of the law. Scientific reports that come out of this study may include your ideas, but they will not use your name or identify you in any way.

10. CONDITIONS WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

The investigator may stop you from taking part in this study if being in the study is unsafe or dangerous to you or if you lose your right to receive medical care at military hospitals. The investigator may also stop you participating if you experience difficulty in following the procedures.

11. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

You have the right to withdraw from this study at any time. If you decide to stop taking part in this study, you should tell the principal investigator as soon as possible; by leaving this study at any time, you in no way risk losing your right to medical care.

12. RECOURSE IN THE EVENT OF INJURY

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, you should contact the Director of Human Research Protections Program at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301) 295-9534. This office can review the matter with you, can provide information about your rights as a subject, and may be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301) 295-3028.

CONTACT FOR QUESTIONS OR PROBLEMS

If you have questions about this research, you should contact Andrew J. Waters, Ph.D. the person in charge of the study. His phone number at USUHS is 301 295-9675. Even in the evening or on weekends, you can leave a message at that number. If you have questions about your rights as a research subject, you should call the Director of Human

Research Protections Program at USUHS at (301) 295-9534. She is your representative and has no connection to the researcher conducting this study.

SIGNATURE OF RESEARCH PARTICIPANT OR LEGAL RESPRESENTATIVE

You have read (or someone has read to you) the information in this consent form. You have been given a chance to ask questions and all of your questions have been answered to your satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

_____ _____

Participant's Signature Date

_____

Participant's Printed Name

SIGNATURE OF INVESTIGATOR/RESEARCH TEAM MEMBER

You have explained the research to the participant, or his/her legal representative, and answered all of his/her questions. You believe that the volunteer subject understands the information described in this document and freely consents to participate.

_____

Investigator's/Research Team Member's Signature Date (must be the same as the participant's)

_____

Investigator's/Research Team Member's Printed Name

SIGNATURE OF WITNESS

Your signature as witness is intended to attest that the information in the consent document and any other information was explained to and apparently understood by the participant, or the participant's legal representative, that questions and concerns were addressed and that informed consent was freely given.

_____

Witness' Signature Date (must be the same as the participant's)

_____

Witness' Printed Name

Appendix E: Demographics Questionnaire

Q1. What is your date of birth? __ __ / __ __ / __ __ __ __ mm / dd / yyyy

2098 Refuse to Answer (Year)

Q2. What is your gender?

1 Male

2 Female

Q3. What is your present marital status? (Choose one)

1 Single

2 Married
3 Divorced
4 Widowed
5 Living with significant other
6 Separated
8 Refuse to Answer

Q4. How many years of education have you completed? (Choose one)

01 1 (Elementary School)
02 2 (Elementary School)
03 3 (Elementary School)
04 4 (Elementary School)
05 5 (Elementary School)
06 6 (Middle School)
07 7 (Middle School)
08 8 (Middle School)
09 9 (High School)
10 10 (High School)
11 11 (High School)
12 12 (High School)
13 13 (Some College)
14 14 (Vocational or Community College Degree)
16 16 (Four Year College Degree)
17 17 (Some Postgraduate Work)
18 18 (Postgraduate Degree; Master Degree)
20 20 (Postgraduate Degree; M.D., Ph.D., DDS, Dr.P.H., etc.)
98 Refuse to Answer

Q5. Are you of Hispanic/Latino origin?

1 Yes

0 No
8 Refuse to Answer

Q6. What category best describes your race? (Choose one)

1	Anglo American/Euro American/White
2	African American/Black
3	Asian American
4	Native of Hawaii or other Pacific Islander
5	Native American or Alaska Native
6	Mixed Race
7	Other
8	Refuse to Answer

If Q6 is equal to 8 or Q6 is less than 7, then skip to Q8.

Q7. Please specify your race.

_____

Q8. Do you receive Medicare, Medicaid, or Medical Assistance currently?

1	Yes
0	No
7	Don't Know
8	Refuse to Answer

Q9. Do you have private insurance or group insurance?

1	Yes
0	No
7	Don't Know
8	Refuse to Answer

Q10. What is you total family income per year, before taxes? (Choose one)

01	Less than $10,000 per year or less than about $833 per month
02	$10,000 to $19,999 per year or less than about $1250 per month
03	$20,000 to $29,999 per year or less than about $2083 per month
04	$30,000 to $39,999 per year or less than about $2916 per month
05	$40,000 to $49,999 per year or less than about $3750 per month
06	$50,000 to $59,999 per year or less than about $4583 per month
07	$60,000 to $69,999 per year or less than about $5416 per month
08	$70,000 to $79,999 per year or less than about $6250 per month
09	$80,000 to $89,999 per year or less than about $7083 per month
10	$90,000 to $99,999 per year or less than about $7916 per month
11	$100,000 or more per year or more than $8333 per month
98	Refuse to Answer

Q11. **Generations in the U.S.** Please choose the best response: (Choose one)

1	I'm an immigrant of the US
2	I was born in the US
3	One of my parents and I were born in the US (the other parent immigrated)
4	My parents and I were born in the US
5	My grandparents, my parents, and I were born in the US
6	My great-grandparents and ancestors were born in the US
8	Refuse to Answer

If Q11 is greater than 1, then skip to Q13.

Q12. What year did you immigrate to the US?

____
yyyy

2098 Refuse to Answer (Year)

Q13. **Employment Status.** Please choose the best response: (Choose one)

01	Regular full-time (30 or more hours per week)
02	Regular part-time (less than 30 hours per week)
03	Unemployed, currently *looking* for work
04	Unemployed, currently *NOT looking* for work
05	Homemaker
06	Student
07	Retired
08	Unable to work or disabled
09	Other
98	Refuse to Answer

If Q13 is less than 9, then skip to Q15.

Q14. Please specify your employment status.

_____

Q15. In the past 30 days, what was the primary source of your income? (Choose one)

1	A job
2	Unemployment Benefits
3	VA/Disability/Social Security Income
4	Welfare/Food Stamps/Aid to Family with Dependent Children
5	Alimony or Child Support
6	Spouce/partner is main source of income
8	Refuse to Answer

Appendix F: Smoking Related Questionnaires

Smoking History Questionnaire

About how old were you when you first started smoking at least 1 cigarette a day? _____ **years old**

About how old were you when you started smoking regularly **everyday**? _____ **cigarettes a day**

How many cigarettes do you smoke on a **normal day**? _____ **cigarettes a day**

	Definitely not	**Probably not**	**Possibly**	**Probably**	**Definitely**
Do you think you are addicted to smoking?	☐	☐	☐	☐	☐

Are you seriously thinking of quitting smoking?

☐ Yes, within the next 30 days

☐ Yes, within the next 6 months

☐ No, not thinking of quitting

	Yes	**No**
Have you used any other tobacco products (i.e., cigars, pipes, smokeless tobacco, bidis, cloves)?	☐	☐

Describe:

	Yes	**No**
Have you ever made a serious and deliberate attempt to **STOP SMOKING** cigarettes completely?	☐	☐

If so, how many times?

_____ times

In the **last year**, how many times have you quit smoking for at least 24 hours?

_____ times

How hard was it for you to quit smoking on your most recent attempt?

	Easy	**Slightly Difficult**	**Difficult**	**Very Difficult**

How severely did you experience any of the following symptoms below in your most recent attempt to quit smoking? Choose the answer that most reflects the severity of each symptom.

	Not at all	**Mild**	**Moderate**	**Severe**	**Very severe**
Cravings for cigarettes	1	2	3	4	5
Irritability	1	2	3	4	5
Nervousness	1	2	3	4	5
Difficulty concentrating	1	2	3	4	5
Physical symptoms	1	2	3	4	5
Difficulty sleeping	1	2	3	4	5

Fagerstrom Test for Nicotine Dependence

	0	1	2	3
1. How soon after you wake up do you smoke your first cigarette?	After 60 Minutes	31 – 60 minutes	6-30 minutes	Within 5 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, cinema, etc?	No	Yes		
3. Which cigarette would you hate most to give up?	All others	The first one in the morning		
4. How many cigarettes/day do you smoke?	10 or less	11-20	21-30	31 or more
5. Do you smoke more frequently during the first hours of waking than during the rest of the day?	No	Yes		
6. Do you smoke if you are so ill that you are in bed most of the day?	No	Yes		

Smoking Diary

Study ID:_____

Tobacco Use Record Form

Instructions for Participant:

- **Complete this form each day.**
- **Just before going to sleep, indicate how many cigarettes you have smoked that day.**
- **Be honest… Accurate information is important!**

I agree to complete this form every night. I will provide information that is as accurate as possible.

SIGNATURE AND DATE:

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1							
Week 2							
Week 3							

Adapted Wisconsin Smoking Withdrawal Scale, Difficulty Concentrating Subscale

Please answer the following questions based on how you feel or what you are noticing RIGHT NOW!

0	*1*	*2*	*3*	*4*
Strongly Disagree	*Disagree*	*Feel Neutral*	*Agree*	*Strongly Agree*

My level of concentration is excellent.

0 1 2 3 4

It is hard to pay attention to things.

0 1 2 3 4

It is difficult to think clearly.

0 1 2 3 4

Difficulty Concentrating Summary Item

Right now, I am having difficulty concentrating.

1 2 3 4 5 6 7 8 9 10 11

NO!! YES!!

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