



WITH TOBACCO USE RESEARCH CENTERS

Advancing Transdisciplinary Science and Policy Studies

The Networker

Emerging Science: TTURC Style

By Robin Mermelstein

As the TTURCs pass the midpoint in their development, some of the preliminary results of the individual projects as well as some of the collaborative efforts are becoming available. Feature stories in this newsletter highlight the broad array of research conducted at the centers. Hallmarks of these studies include the recognition of the heterogeneity of smokers and the need to identify subgroup differences among smokers that might guide future interventions. Several of the research projects are also innovative in their use of newer technologies, from multiple disciplines, that

help to address questions in a more detailed or fine-grained manner than has previously been possible. These advancements include novel uses of statistical techniques as well as imaging technologies; in-vivo, real-time assessments; and genetic testing. Strengths of the TTURCs also include the ability to leverage an infrastructure and on-going data collection efforts to address time-sensitive research questions, such as the effect of major events (e.g., September 11) on smoking. We look forward to seeing the results of the studies and others at the centers, and their impact on changing practice and policy.

TTURC Partners Conference a Great Success!

By Nicole Greenway

The latest TTURC Partners Conference was a great success. During the June, 2002 meeting in Providence, RI, sixty TTURC researchers met to discuss their manuscript drafts for the TTURC Monograph Series. During the conference, there was plenty of interesting discussion revolving around defining transdisciplinarity and how to use appropriate discipline-specific terminology. Authors used these types of discussions to enhance their own papers, while also trying to incorporate common terminology throughout the Monograph Series. The papers will be submitted to the Society for Research and Nicotine Journal, Nicotine and Tobacco Research with plans for publication as a

supplemental issue.

The Monograph series is currently designed to include three process papers that demonstrate the unique methods and opportunities that arise from transdisciplinary research, as well as four topic specific papers.

In addition, Bill Trochim, Ph.D., from Cornell and an NCI Visiting Scientist, also presented methods and tools that will be used to evaluate the initiative. If you would like to check out the evaluation process, go to Trochim's website (<http://omni.cornell.edu/ttunc>)

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Reducing Harm of Tobacco With Novel Approaches to Treatment

By Val Marti Shultzabarger

Scientists at UMN TTURC are discovering that there may be new alternatives on the horizon to help individuals reduce smoking as a transitional step to quitting.

The effects of high dose nicotine on nicotine self-administration in rats is being investigated by Paul Pentel, Ph.D., professor of medicine and pharmacology in the Medical School. In so doing, Pentel is able to examine the efficacy and safety of nicotine replacement doses that are higher than those smokers normally achieve through smoking.

By using an animal model that simulates smoking in humans, Pentel's lab is finding that high doses of nicotine suppress the amount of nicotine rats self-administer. Thus far, "the high doses are not only effective in reducing nicotine self-administration, but also appear to be well tolerated by the rats," says Pentel. This work is being extended in a study by Dorothy Hatsukami, Ph.D., director of UMN TTURC, specifically examining effects of high dose nicotine on cigarette smoking in humans.

Knowing that smoking during pregnancy is associated with a variety of adverse effects including increased mortality among newborns, Pentel, in a separate study, is also exploring the ability of vaccination to reduce fetal exposure to nicotine. Female rats are vaccinated

"To date we have been examining the effects of continuous nornicotine infusion on nicotine self-administration in rats. Nornicotine appears to reduce nicotine self-administration in a dose dependent fashion with the highest dose producing a 50% decrease."
- Mark LeSage

against nicotine, then are mated. When pregnant, the mothers receive a dose of nicotine and the fetus' level of nicotine exposure is measured.

Preliminary data show that the vaccination reduces nicotine distribution to the fetal brain by 44%. This is a promising finding, given that the fetal brain is the target of many of nicotine's adverse prenatal effects.



Paul Pentel, Ph.D.

In a pilot study, Mark LeSage, Ph.D., associate investigator in the Department of Medicine, is examining the potential use of nornicotine (a nicotine byproduct) as a pharmacotherapy for smoking cessation. Since nornicotine produces behavioral effects that are similar to nicotine, it may provide an alternative substitution therapy. "To date we have been examining the effects of continuous nornicotine infusion on nicotine self-administration in rats. Nornicotine appears to reduce nicotine self-administration in a dose dependent fashion with the highest dose producing a 50% decrease," LeSage said.

Pentel and LeSage's work will continue to focus on the relationship of individual differences and the efficacy of nicotine replacement in reducing nicotine self-administration in rats. Preliminary findings suggest that the dose used in nicotine replacement therapy may need to be tailored to the individual's overall level and patterns of smoking to maximize efficacy. Future research will examine the relationship of gender differences, and pregnancy to the efficacy of nicotine replacement in rats self-administering nicotine. These data will be crucial in determining how to design alternative therapies that address reducing tobacco harm in men, women and their children.

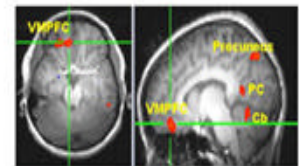
Using fMRI to Study Cue-induced Nicotine Cravings

By Maggie Angle

Through the utilization of modern imaging techniques, TTURC researchers at the University of Pennsylvania are working to create a "brain signature" for cue-induced nicotine craving. Research shows that exposure to smoking-related stimuli and subsequent cigarette craving often precede smoking relapse. In the *Perfusion fMRI of Cue-Induced Nicotine Craving* pilot project perfusion functional magnetic resonance imaging (fMRI) is being used to characterize the regions of the Central Nervous System (CNS) and neurochemistry associated with cue-induced nicotine craving.

"Knowledge of the brain substrates specifically acti-

vated by cigarette-related stimuli may aid in the search for viable pharmacotherapies to help smokers remain abstinent for life," said lead investigator Teresa R. Franklin, Ph.D. Franklin, an Assistant Professor of Psychiatry at the University of Pennsylvania, believes this pilot project represents the first time that



Neural activation in smokers to nicotine cues compared to non-nicotine cues, using perfusion fMRI with AFNI (N=2, p<.02). Abbrev. VMPFC, ventromedial prefrontal cortex; PC, posterior cingulate; Cb, cerebellum

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Using Technology to Understand and Prevent Smoking Relapse

By Gloria Meyers

Although numerous studies on effective smoking cessation treatment have been conducted, we still know little about exactly what happens during a quit attempt and how and why some smokers relapse. Previous methodologies rely on subject memory, I.e., paper and pencil surveys. Advances in technology have opened the door to instantaneous recording of a variety of factors, including withdrawal symptoms, stressors in the environment, and physiological, psychological and social triggers.



Electronic diary used to gather real-time cessation information.

Three major studies at the University of Wisconsin TTURC include the use of technological devices to record in real-time what a study participant experiences during a quit attempt.

The Measurement of Tobacco Dependence study seeks to develop new measures of tobacco dependence. Currently, a 68-item questionnaire, the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68), is being validated in Milwaukee. Participants, after completing the questionnaire, are provided with bupropion and/or nicotine gum as aids in their quit attempt. Using cell

"These technologies can provide data in quality and quantity unheard of in the past. I believe they will help us understand the heterogeneity of withdrawal and thereby speed us toward a greater variety of treatments for tobacco dependence." - Tim Baker

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Applying Contingency Management Techniques to Improve Smoking Abstinence

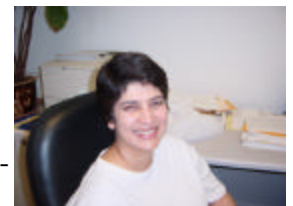
By Pem McNerney

When Suchitra Krishnan-Sarin, Ph.D., an Assistant Professor of Psychiatry at Yale University School of Medicine and a principal investigator with CEN-TURY/TTURC, was designing her study on evaluating abstinence effects in high-risk smokers, she wanted to use a powerful behavioral approach to help research subjects quit smoking. She decided she would use contingency management (CM) techniques to enhance abstinence rates. CM of substance use behavior refers to a method of reducing substance use through incentives and tangible reinforcers that are contingent on reduction in use or abstinence. The overall goal of Krishnan-Sarin's study is to help determine the nature, intensity and timing of abstinence effects in smokers who have a particularly hard time quitting, including women, drinkers and people who have depressive symptoms.

"The innovative piece of our program is that we combine a well-established contingency management paradigm with a strong behavioral smoking cessation program based on the Agency for Health Care and Policy Research guidelines" —Suchitra Krishnan-Sarin

CM is not new to the field of substance abuse. It has been used in a variety of treatment and non-treatment experimental programs for tobacco and other substances. What makes her study unique is that she is using CM in conjunction with intensive behavioral smok-

ing cessation counseling. "Many of the past programs that have used contingency management for smoking cessation have not had strong behavioral support paradigms," Krishnan-Sarin said. "The innovative piece of our program is that we combine a well-established contingency management paradigm with a strong behavioral smoking cessation program based on the Agency for Health Care and Policy Research guidelines."



Suchitra Krishnan-Sarin, Ph.D.

Participants in Krishnan-Sarin's study join a one-month intensive smoking cessation program that teaches them how to quit and prevent relapse. Participants receive CM along with intensive, daily behavioral support during the first week followed by behavioral support alone on a tapering-off schedule during weeks 2,3 and 4. The research program also uses biochemical techniques to verify abstinence from cigarettes.

Krishnan-Sarin is very pleased with the numbers. At the end of the first week, using an initial sample of 28 smokers, the quit rates are at 91.7 percent. With removal of the CM techniques during the next three weeks, but with continuation of the behavioral support on a lighter schedule, the rates do decrease. However, by the end of the fourth week, they are still relatively high at 51 percent.

Applying Generalized Estimating Equation to Smoking Data

By Suzanne Moriarty

Until he joined the TTURC as PI of the Statistical Sciences Core, George Papandonatos, Ph.D., Assistant Professor of biostatistics at Brown's Center for Statistical Sciences, had done little direct work in either tobacco dependence research or in genetics. He now increasingly devotes time and intellectual effort to both areas as a major focus of his academic career.



George Papandonatos, Ph.D.

Papandonatos has explored the benefits and remarkable results of an innovative analytical approach -- applying Generalized Estimating Equation methodology to smoking data of genetically related individuals. He clarifies, "the approach itself is not new, but this application is, especially in that we went beyond the usual twin, monozygotic (MZ) and di-zygotic (DZ), design and analyzed full-(FS), half- (HS) and unrelated (NR)-sibs."

Utilizing the genetic subsample from the first two waves of the National Longitudinal Study of Adolescent Health, the research team used second order Generalized Estimating Equation methodology to estimate the longitudinal progression of smoking, defined in discrete stages (Never Smokers, Experimenters, Intermittent, Regular/Established), among 2,199 adolescent sib-

ling pairs (256 MZ, 405 DZ, 929 FS, 328 HS, 281 NR) as a function of sib-pair type.

Papandonatos explains the significance, "our model can handle two, possibly distinct, sets of covariates: one for the mean response, the other for the association. Most other data analytic methods cannot fit regression models to the association, only to the mean response." This flexible modeling framework can be easily extended to handle additional variables at both the individual and sib-pair levels. It allows genetic and environmental influences, and their interaction to be assessed directly in terms of smoking phenotypes, rather than in a latent scale of smoking dependence. This enhances the interpretability of regression coefficients. This is a significant advance in statistical methodology that complements and extends standard techniques for analyzing genetically informative designs.

"This contribution to the field would not have been possible without our TTURC, since it was the bringing together of scientists and statisticians from several areas—genetics, developmental psychology, and tobacco addiction research that prompted it."—Dave Abrams

David Abrams, Ph.D., PI, states "This contribution to the field would not have been possible without our TTURC, since it was the bringing together of scientists and statisticians from several areas - genetics, developmental psychology, and tobacco addiction research - that prompted it."

Reducing Harm continued...

(Continued from page 2)

perfusion fMRI is being used to study cue-induced nicotine craving.

Participants in this study are shown two videos: one containing numerous smoking cues and the other containing no such cues. At two-minute intervals throughout each video, participants are asked to report their current desire for a cigarette. During these sessions, an arterial spin labeled (ASL) perfusion fMRI is used to map changes in brain perfusion, or the delivery of oxygen and nutrients to brain tissue through blood flow. This technique utilizes electromagnetically labeled arterial blood water as an endogenous tracer for measuring cerebral blood flow. Changes in blood flow result in changes in tissue contrast, which MRI scanners measure to identify CNS regions activated by cigarette-related stimuli.

Perfusion fMRI also provides a stable signal for low frequency changes that occur slowly over

"Knowledge of the brain substrates specifically activated by cigarette-related stimuli may aid in the search for viable pharmacotherapies to help smokers remain abstinent for life" -Teresa Franklin

time. Inducing the craving state requires several minutes, thus each cue exposure is several minutes long. The stable signal prevents confounding drift with the signal of interest, leading Franklin to believe that this technique is preferable to blood oxygen level dependent fMRI, which she used previously.

In the future, Franklin plans to examine the effects of bupropion and baclofen on cue-induced CNS activation. This research will seek to determine if medications that blunt neuronal response to cues can also attenuate cue-induced craving and, therefore, possibly be an effective treatment option.

Addressing Adolescent Smoking and Emotional Responses to Trauma

By Louri Groves

Emotions play a critical role in smoking initiation and maintenance, but most tobacco research is conducted by individuals who do not specialize in emotion.

Similarly, little is known about the cognitive appraisals of events associated with tobacco cravings and smoking.

Research conducted by Linda Levine, Ph.D., a national authority on emotion, is investigating the effects of a traumatic life event on adolescents' smoking urges and behavior. Adolescents and their parents will be asked to complete questionnaires concerning their reactions to the terrorist attacks in New York on September 11, 2001.

These questionnaires will assess their emotional reactions, cognitive appraisals, and memories concerning the attacks, as well as the intensity of their urge to smoke and actual smoking behavior. According to Levine, UCI Associate Professor, "We are poised to elucidate the effects of traumatic life events, and the individual differences in emotional responses to trauma, on

"The proposed study will increase our understanding of how adolescents' emotional and cognitive response to events help professionals to develop and evaluate preventative interventions targeted toward groups of teenagers with particular vulnerabilities."—Linda Levine

smoking in adolescences." Levine will draw upon participants who are currently taking part of an ongoing longitudinal study conducted by Larry Jamner, Ph.D. and Carol Whalen, Ph.D. Thus, extensive data is available on their dispositional trait and their typical moods, activities and smoking urges and behaviors.



Linda Levine, Ph.D.

Specifically, the study will assess: (a) how individual differences in emotional reactions, cognitive appraisals and dispositional traits interact to predict adolescents' smoking urges and behavior; (b) gender differences in the types of negative affect associated with adolescent smoking; (c) differences between adolescents and adults in their ability to regulate negative emotions that increase adolescents vulnerability to smoking; and (d) whether intrusive, affectively-intense memories that remain potent over time are associated with increases in smoking.

"The proposed study will increase our understanding of how adolescents' emotional and cognitive response to events help professionals to develop and evaluate preventative interventions targeted toward groups of teenagers with particular vulnerabilities," said Levine.

Using Technology continued...

(Continued from page 3)

phones, they are being contacted during their quit attempt through an *automated voice response messaging system*. Participants are prompted to answer questions about smoking status, withdrawal and stressors using the keypad on their phones.

The Real-Time Response: Assessments of Quitting Processes and Treatment Effects study, being conducted in Madison, uses *electronic diaries* to gather information from participants who are quitting smoking. All participants receive smoking cessation counseling. In addition, some receive bupropion and others do not. Participants carry the hand-held computers and are reminded 4-6 times a day to answer a short questionnaire about their quit attempt.

The Computer-Delivered Smoking Cessation Treatment being conducted in both Madison and Milwaukee uses

technology to assess the quitting process and to provide treatment. A collaborative research study between UW-TTURC researchers and the UW Center for Health Systems Research and Analysis (CHSRA), this trial compares quitting success for participants using bupropion alone and those using bupropion and the specially-designed computer program, "*Quitting Smoking for Life*." The computer program provides information, coping skill training, a chat room, advice from experts and other quit smoking aids. In addition, a required daily check-in includes questions designed to improve our understanding of the quit process.

"These technologies can provide data in quality and quantity unheard of in the past," said Tim Baker, director of the research program. "I believe they will help us understand the heterogeneity of withdrawal and thereby speed us toward a greater variety of treatments for tobacco dependence."

Identifying Adolescent Subcultures at High Risk for Smoking

By Paula Palmer

USC TTURC researchers, headed by C. Anderson Johnson, are finding that rapid sociocultural change and exposure to a multitude of cultures and subcultures in ethnically diverse settings like Los Angeles may affect cigarette smoking initiation in adolescents.



Andy Johnson, Ph.D.

“In our early work,” Dr. Johnson said, “we considered culture in terms of a child’s ethnic identity and country of origin. While that was a reasonable place to start, it probably doesn’t capture the features of culture that may be most important to a young person in a multi-cultural setting like L.A. So now we’re expanding our study to include the information-sharing groups that adolescents belong to – what we also call subcultures or boutique cultures.” Subcultures include many of the activities that are typically associated with adolescence, including, skateboarding, video game playing, going to malls, and hanging out with friends who identify themselves using similar terms (i.e., “jocks,” “gamers,” skaters,” “Cholos,” etc.).

Results from USC researchers suggest that while Latino culture appears to be a protective factor against smoking, Latino adolescents who self-identify as a “Cholo” or “gangster” are more likely to smoke than Latino adolescents who do not identify themselves this way. Thus, it appears that subcultural influences and identification erodes the impact of the traditional culture. Similarly, Asian self-identification also appears to be protective, but findings suggest “skater” self-identification and video game arcade participation decreases the protective influence of Asian culture and increases an adolescents’ risk of smoking.

In each higher risk subculture, the group’s activities seem to take the young person out of the sphere of influence of parents and traditional culture. Not all subcultures enhance smoking risk. For most ethnic groups, involvement in Internet, computer games, video/TV watching, sports, and religious activities are associated with reduced smoking risk. These activities may not take the young person far outside the realm of parental influence.

The USC group is investigating optimal venues and channels for communications targeted to youth sub-

cultures. The group also is exploring potential dispositional characteristics that might increase exposure to and influence by affiliations with high and low risk subcultures.

“In our early work, we considered culture in terms of a child’s ethnic identity and country of origin. While that was a reasonable place to start, it probably doesn’t capture the features of culture that may be most important to a young person in a multi-cultural setting like L.A. So now we’re expanding our study to include the information-sharing groups that adolescents belong to – what we also call subcultures or boutique cultures.”
- Andy Johnson

TTURC News and Happenings

Upcoming Events

September 24-25, 2002—Partners Policy Research Workshop, Chicago, IL

January 28-30, 2003—TTURC Partners Winter Meeting, Santa Fe, NM.

Recent TTURC Publications

Henker, B., Whalen, C.K., Jamner, L.D. & Delfino, R.J. (2002). Anxiety, affect, and activity in teenagers: monitoring daily life with electronic diaries. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 660-670.

Lerman, C., Roth, D., Kaufmann, V., Audrain, J., Hawk, L., Liu, A., Niaura, R., & Epstein, L. (2002). Mediating mechanisms for the impact of Bupropion in smoking cessation treatment. *Drug and Alcohol Dependence*, 67(2), 219-223.

LeSage, M.G., Keyler, D.E., Shoeman, D., Raphael, D., Collins, G., & Pentel, P.R. (2002). Continuous nicotine infusion reduces nicotine self-administration in rats with 23 hour/day access to nicotine. *Pharmacology, Biochemistry & Behavior*, 72, 279-289.

Unger, J.B., Li, Y., Shakib, S., Rohrbach, L.A., Chen, X., Guo, Q., Chou, C.-P., Shan, J., Azen, S., Zheng, H., & Johnson, C.A. (2002). Peer influences and access to cigarettes as correlates of adolescent smoking: A cross-cultural comparison of Wuhan, China and California. *Journal of Preventive Medicine*, 34, 476-484.

Whalen, C.K., Jamner, L.D., Henker, B., Delfino, R.J., & Lozano, J. (2002). The ADHD spectrum and every day life: Experiencing sampling of moods, activities, smoking and drinking. *Child Development*, 73, 209-227