***BRIEF******COMMUNICATION***

**Keeping Quitting in Mind: Working Memory-Related**

**Neural Activity Predicts Future Relapse**

James Loughead, Ph.D., E. Paul Wileyto, Ph.D., Kosha Ruparel, M.S., Mary Falcone, Ph.D., Ryan Hopson, Ruben Gur, Ph.D., and Caryn Lerman, Ph.D.

**Word Count: 1,198**

**Corresponding Author:** James. Loughead, Ph.D., Associate Professor, Department of Psychiatry, University of Pennsylvania, 3535 Market Street, Suite 4100, Philadelphia, PA 19104, Phone: 215-746-7279, Fax: 215-746-7140, Email: loughead@upenn.edu

**ABSTRACT**

The neural mechanisms underlying failed behavior change attempts are poorly understood. Eighty-one smokers completed two fMRI sessions (smoking satiety vs. 24hr abstinent) followed by counseling and a monitored quit attempt. Biochemically confirmed failure within 7 days was predicted by decreased left dorsolateral prefrontal cortex and increased posterior cingulate cortex activation (abstinence minus smoking), with significant contributions beyond standard clinical measures. Cross validation procedures demonstrated 83.3% correct classification of relapsers.

Maladaptive behaviors such as tobacco use, unhealthy diet, and physical inactivity have far reaching health and economic implications. Yet, many unhealthy behaviors are difficult to change even with the best available interventions. Emerging research suggests that impairments in executive cognitive function play a central role in failed attempts at behavior change[1](#_ENREF_1). Elucidating the neural underpinnings of these processes is a critical step in developing neuroscience-based treatments. We addressed this question by studying the neural mechanisms underlying early relapse in treatment-seeking smokers.

We predicted that maladaptive changes in working memory related neural activity would predict future relapse. Even brief abstinence from smoking produces impairments in working memory that are accompanied by reduced activity in regions within the executive control network [e.g., dorsolateral prefrontal cortex (DLPFC), medial frontal/cingulate gyrus (MF/CG)], decreased suppression of activity in regions within the so-called default mode network [e.g., posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC)][2-4](#_ENREF_2) and dysregulated inter-network connectivity at rest[5](#_ENREF_5). Effective medications reverse these changes in abstinent smokers[3](#_ENREF_3). To our knowledge, no study has examined whether working memory-related neural activity predicts relapse to smoking.

Eighty-one treatment-seeking smokers completed two blood oxygen level dependent (BOLD) fMRI scans while performing a visual N-back task: one session during smoking satiety and the other after 24 hours of biochemically confirmed abstinence (order counterbalanced). Approximately 1-2 weeks after imaging, participants received brief standardized smoking cessation counseling and set a quit date. The primary outcome was short-term relapse defined as any smoking lapse during the first 7 days after the target quit date, biochemically confirmed by the presence of the nicotine metabolite cotinine. Because most smokers who relapse do so within the first 7 days, this measure is a well-validated indicator of long-term smoking status[6](#_ENREF_6). Sixty-two smokers relapsed and 19 quit successfully for this period. Of this sample, five relapse and four quit data sets were excluded due to poor quality (RMS mean relative motion > 0.4, total non-responses > 66%). In the final sample of 72 smokers, mean % signal change was extracted from *a priori* regions of interest[2-5](#_ENREF_2): bilateral DLPFC, MF/CG, PCC, and vmPFC (Supplementary Methods). Based on prior work showing the greatest nicotine abstinence effects at the highest working memory load[3](#_ENREF_3), [4](#_ENREF_4), [7](#_ENREF_7), we examined BOLD signal acquired during performance of 3‑back trials. Twenty-four hour abstinence challenge produced the expected effects in behavior and brain signal (supplemental methods).

Forward stepwise logistic regression was used to predict dichotomized 7-day relapse. Sex, age, and nicotine dependence level[8](#_ENREF_8) were selected as baseline candidate predictors of relapse. Change scores for paired data collected during abstinence challenge [mood[9](#_ENREF_9), withdrawal[10](#_ENREF_10), craving[11](#_ENREF_11), and brain signal (see above ROIs)] were also included in the model. We required age and nicotine dependence to be entered based on clinical relevance; sex was non-significant, and allowed to drop out. Relapse was predicted by older age (OR=1.072, CI95% 1.010 – 1.139, P=0.02) and greater withdrawal difference (OR=1.173, CI95% 1.009 – 1.365, P=0.04). Two BOLD variables added significantly to the predictive model: decreased activation in left DLPFC (OR=0.145, CI95% 0.028 – 0.742, P=0.02), and greater activation (i.e. less suppression) in the left PCC (OR=3.449, CI95% 1.051 – 11.132, P=0.04) (Figure 1).

To estimate the predictive value of the relapse model, we used receiver operating characteristic (ROC) analysis to calculate area under the curve (AUC). The model with brain signal (full model) yielded an AUC of 81%, a significant improvement over clinical predictors alone (67%; X2(1)=4.06, p<0.05) (Figure 2). This corresponds to 87.5% correct classification at the optimal cut-off value. The full model was further validated using resampling methods. Bootstrapping[12](#_ENREF_12) generated 1000 replicates of the data and conducted model selection on each replicate. Accounting for age and nicotine dependence and sampling with replacement, the most frequently selected variables were withdrawal, left DLPFC and PCC – the same variables identified by stepwise procedures. To examine the model’s potential for prediction in individual cases, we performed leave-one-out cross-validation (LOOCV)[13](#_ENREF_13). Compared to 81% AUC for the full model, LOOCV achieved an AUC of 71%; at an optimal cut-off value this corresponds to 83.3% correct classification (4.8% reduction).

These results provide novel evidence that aberrant neural activity underlying working memory deficits predict failed attempts to quit smoking. Decreased left DLPFC activation, and reduced suppression of left PCC during 24-hour abstinence challenge predicted relapse during a future quit attempt --beyond the contributions of standard clinical variables alone. Of note, these brain regions were also the most sensitive to abstinence challenge. When accounting for the expected reduction in model accuracy in an out-of-sample (i.e., individual subject) prediction, the optimal ROC cut-off value continued to deliver excellent performance (83.3%) consistent with other clinically relevant predictive models[14](#_ENREF_14). The left hemisphere lateralization of these effects is consistent with prior findings in abstinent smokers[7](#_ENREF_7).

These data suggest that the ability to exert top-down cognitive control during the early phase of a quit attempt may distinguish successful quitters from those who fail. Left DLPFC activation is essential to maintain goal-directed attention and behavior, particularly in the face of competing attentional demands[15](#_ENREF_15). Indeed, when DLPFC is engaged, activation in subcortical regions can be modulated to reduce the drive for rewards such as smoking[16-18](#_ENREF_16). Reciprocal deactivation of PCC, a central hub in the default mode network, is also integral to shifting attention away from goal-irrelevant processes, such as intrusive thoughts about wanting to smoke[5](#_ENREF_5), [19](#_ENREF_19).

The current study reveals the significant contribution of neural activity to prospectively measured behavioral relapse. The relatively small sample of quitters is a natural consequence of behavioral counseling without medication. A replication sample is required to validate our model, however the observed shrinkage in AUC with the LOOCV procedure suggests that our model is not inflating predictive power. While broad implementation of neuroimaging assessment is not currently clinically or economically feasible, the mechanisms identified are potential therapeutic targets for neuroscience-based interventions to promote behavior change. Techniques that augment DLPFC function, support neuronal plasticity, and improve the executive regulation of unhealthy behaviors are targets that can be pursued with cognitive remediation, novel pharmacological agents and transcranial stimulation [20](#_ENREF_20). Regardless of therapeutic approach, models sensitive to relapse risk can guide the refinement of efficacious tobacco dependence treatment.

**Figure 1** **(a)** Visualization of functionally defined N-back regions of interest in the left dorsolateral prefrontal cortex (DLPFC) and posterior cingulate cortex (PCC), p<0.001, corrected. **(b)** Forward stepwise logistic regression retained the left DLPFC, left PCC and withdrawal scores in the predictive model. Greater abstinence induced change in withdrawal (increased), left DLPFC signal (reduced activation), and PCC signal (less deactivation) was predictive of relapse.

**Figure 2** ROC curves for three predictive models of 7 day quit status. The full model (black) includes clinical, withdrawal and brain variables, yielding an AUC of 81%. Clinical predictors alone (light gray) achieved an AUC of 73% and the intermediate model, using only clinical and withdrawal scores, an AUC of 67% (dark gray).

**ACKNOWLEDGEMENTS**This research was supported by grants from the National Cancer Institute and National Institutes on Drug Abuse (P50CA143187 and R03DA027438).

**AUTHOR CONTRIBUTIONS**

The following authors participated in study design (JL, RG, CL), data processing and analysis (EPW, KR, MH, RH, JL), and manuscript writing (JL, CL). All authors reviewed, commented, and approved the manuscript.

**COMPETING FINANCIAL INTERESTS**

Dr. Leman has served as a consultant and/or received research funding from Pfizer.

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