PREDICTING SMOKING RELAPSE FROM WORKING MEMORY-RELATED NEURAL ACTIVITY

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Introduction

Tobacco dependence has far reaching health and economic consequences.

Smokers attempting to quit commonly report “difficulty concentrating”.

Abstinent smokers exhibit deficits on measures of executive function, including working memory.

Working memory, a key element of executive function, is essential to maintaining goal-directed behaviors.
Research Program

• Characterize nicotine withdrawal-related working memory deficits using BOLD fMRI
• To evaluate the effect of a “best in class” treatment (varenicline) on abstinence induced WM deficits and underlying brain signal
• To test whether these neural signals predict smoking relapse

Allenby et al., Addiction Biology, 2019; Allenby et al., Nicotine Tob Res, 2019; Ashare et al., Psychopharmacology, 2016; Loughead et al., Neuropsychopharmacology, 2015; Falcone et al., Addiction Biology, 2014; Lerman et al., JAMA Psychiatry, 2014; Loughead et al., Biological Psychiatry, 2010; Loughead et al., Molecular Psychiatry, 2009.
Faster reaction time (efficiency) on the N-back working memory task after 72 hours of abstinence predicts 7-day quitting (p=0.01; $r^2=.15$)
N=63 within-subject, session effect on WM performance and BOLD signal change p<0.001, corrected.

Falcone et al., *Addiction Biology*, 2013
Visual N-Back Working Memory Task. Main effects of treatment (varenicline, placebo) observed in all three ROIs (p<0.05 corrected).

Loughead et al, *Biological Psychiatry*, 2010
Abstinence challenge vs. smoking will:

Decrease activation in DLPFC, MF/CG
Reduced deactivation in the PCC, vmPFC

Abstinence-induced changes in WM-related BOLD fMRI signal will predict the likelihood of early smoking relapse beyond standard clinical and behavioral measures.
Baseline candidate predictors: Sex, age, and nicotine dependence

Change scores for paired data collected during abstinence challenge:

MNWS, QSU-Brief, PANAS Positive, PANAS Negative, right DLPFC, left DLPFC, MF/CG, vmPFC, and PCC

Age and nicotine dependence entered based on clinical relevance; sex was non-significant, and allowed to drop out.

Using Bootstrapping procedures, PPC, Left DLPFC, and withdrawal scale were most frequently retained.
Ideal cut point corresponds to 83.3% correct classification. LOOCV achieved an AUC=0.71. The 12% shrinkage observed in the LOOCV result corresponds to a 4.8% reduction in correct classification at the optimal cut-off value.

Loughead et al., *Neuropsychopharmacology*, 2015
Summary

Altered WM-related signal in early abstinence differentiates successful vs. unsuccessful quitters.

Changes are characterized by decreased signal in left DLPFC and increased PCC (less deactivation) for abstinence vs. smoking satiety sessions.

81% AUC for predicting relapse, significant improvement over clinical variables only.

Whole brain analysis also identified left DLPFC.
Limitations:

- Model shrinkage (12%) but within expected range.

- Unaided quit attempt with low success rate.

- Short term cessation, however 7-day quit is predictive of 6-month quit (Ashare et al., 2013).
Abstinence significantly alters stress reactivity in the left inferior frontal gyrus.
Abstinence-induced change in ACC during cue reactivity
**Integrated Model**

**FIGURE 1: INTEGRATED BRAIN-BEHAVIOR MODEL**

- Abstinence-induced changes in working memory, cue- and stress-reactivity predict relapse (Aim 1)
  - Cue-Reactivity (smoking cue task)
  - Brain Systems (ACC, Insula, VS/NAC)

- Working memory buffers effects of cue- and stress-reactivity on relapse (Aim 2)
  - Working Memory (N-back task)
  - Brain Systems (DLPFC, MF/CG, PCC, vmPFC)
  - Stress Reactivity (imagery task)
  - Brain Systems (ACC, Insula, Amygdala, VS/NAC)

**RELAPSE**

- Craving
- Negative affect
Implications

Left DLPFC as a target for intervention

WM-related neural activation as a biomarker for predicting relapse risk in clinical practice?

- validate in large sample with alternate therapies and longer follow-up
- develop feasible clinical strategy (cost/benefit ratio)

Establish biomarker validation criteria
- Reproducibility
- sensitivity to intervention
- prediction threshold
- cost effectiveness  
  (Bough et al, Clin Pharm Ther, 2013)